The Alzheimer's Drug Discovery Foundation presents:

12TH INTERNATIONAL CONFERENCE ON ALZHEIMER'S DRUG DISCOVERY

September 26-27, 2011

Jersey City, NJ

www.alzdiscovery.org

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WELCOME

On behalf of the Alzheimer's Drug Discovery Foundation (ADDF), I am pleased to welcome you to our *12th International Conference on Alzheimer's Drug Discovery*.

For more than a decade now, our annual meeting has brought together scientists intent on accelerating the development of treatments for Alzheimer's disease and related dementias, while creating opportunities for networking between academia, government, and 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 the disease.

We are deeply grateful to our generous sponsors whose support makes this meeting possible: Pfizer Inc.; Merck Research Laboratories; Lilly USA, LLC; Elan Pharmaceuticals, Inc.; Allon Therapeutics, Inc.; NeuroPhage Pharmaceuticals, Inc.; JSW Lifesciences GmbH; Abbott Laboratories; and Genentech. We would also like to thank our exhibitors and 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.

I am pleased to report that we received a record number of scholarship applications to attend this year's meeting. Engaging the next generation of research scientists in the field is more important than ever so please visit their poster presentations. We are proud of their efforts and encourage them to continue pursuing their work in the field.

To help us plan an even better conference in 2012, please complete the survey to provide us with feedback and suggestions.

Welcome, once again, to the *12th International Conference on Alzheimer's Drug Discovery*!

Best Regards,

Howard Fillit, MD
Executive Director
Alzheimer's Drug Discovery Foundation

ABOUT THE ALZHEIMER'S DRUG DISCOVERY FOUNDATION

Alzheimer's Drug Discovery Foundation

MISSION

The Alzheimer's Drug Discovery Foundation's (ADDF) sole mission is to rapidly accelerate the discovery and development of drugs to prevent, treat and cure Alzheimer's disease (AD), related dementias and cognitive aging.

The Alzheimer's Drug Discovery Foundation was established in 2004 to expand upon the programs initiated by the Institute for the Study of Aging (ISOA) Inc., a private foundation founded by the Estée Lauder family in 1998. We use a venture philanthropy investment model to bridge the global funding gap between basic research and later-stage development, recycling any return on investment to support new research.

The ADDF has granted more than $50 million to fund over 340 Alzheimer's drug discovery programs and clinical trials in academic centers and biotechnology companies in 18 countries. Scientists funded by the ADDF have tested over 30 new drugs in people with Alzheimer's disease. Subsequent to the ADDF's critical initial funding, our grantees have received commitments of over $2 billion in follow-on funding from government, pharmaceutical companies and venture capital firms to further advance their drug research.

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 winter, 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 around a relevant topic in the field of neurodegeneration.

PROGRAM

Monday, September 26	
8:00 – 8:30am	**Registration & Continental Breakfast**
8:30 – 8:50	**Welcome & Opening Remarks** Howard Fillit, MD, Alzheimer's Drug Discovery Foundation
8:50 – 9:30	**PLENARY: From Academic Discovery Towards an FDA Approval for a Novel Amyloid Imaging Agent** Daniel M. Skovronsky, MD, PhD, Avid Radiopharmaceuticals, Inc.
I. Targeting Tau for Alzheimer's Disease and Related Dementias Chair: Illana Gozes, PhD, Allon Therapeutics Inc.	
9:30 – 9:35	**Session Overview** – Illana Gozes, PhD, Allon Therapeutics Inc.
9:35 – 9:55	**The Discovery and Preclinical Progress of the Neuroprotective Peptide, *davunetide*, in the Treatment of Tauopathies** Illana Gozes, PhD, Allon Therapeutics Inc.
9:55 – 10:05	*Q&A*
10:05 – 10:25	**Modulating the Hsp70/DnaJ Protein Interface to Dictate Triage Decisions for Tau** Chad Dickey, PhD, University of South Florida
10:25 – 10:35	*Q&A*
10:35 – 11:05	**BREAK**
11:05 – 11:25	**Developing a Tau Imaging Agent for Alzheimer's Disease** Jeff Kuret, PhD, Ohio State University
11:25 – 11:35	*Q&A*
11:35 – 11:55	**Targeting Tau Oligomers through Immunotherapy** Rakez Kayed, PhD, University of Texas Medical Branch
11:55 am – 12:05 pm	*Q&A*
12:05 – 12:25	**Tau Clearance by Autophagy** Karen Duff, PhD, Columbia University
12:25 – 12:35	*Q&A*
12:35 – 1:30	**LUNCH & POSTER SESSION**
II. Inflammation, Chaperones and Novel Targets Chair: D. Martin Watterson, PhD, Northwestern University	
1:30 – 1:35	**Session Overview** – D. Martin Watterson, PhD, Northwestern University
1:35 – 1:55	**Design and Refinement of Novel Small Molecule Compounds Targeting Proinflammatory Cytokine Overproduction: A Potential Disease-Modifying Therapeutic Approach to CNS Diseases** D. Martin Watterson, PhD, Northwestern University
1:55 – 2:05	*Q&A*
2:05 – 2:25	**Optimizing New Drug Candidates for Protein Disulfide Isomerase, A Novel Target for Neurodegenerative Diseases** Donald C. Lo, PhD, Duke University Medical Center
2:25 – 2:35	*Q&A*
2:35 – 2:55	**Proof-of-Concept That Small Molecule Structure Correctors Are Capable of Abolishing the Detrimental Effects of Apolipoprotein E4 in Vitro by Inhibiting Domain Interaction** Robert W. Mahley, MD, PhD, Gladstone Institute of Neurological Disease and University of California, San Francisco
2:55 – 3:05	*Q&A*
3:05 – 3:35	**BREAK**
3:35 – 3:55	**Tau Lowering Agents for the Treatment of Alzheimer's Disease** Allen Reitz, PhD, ALS Biopharma, LLC
3:55 – 4:05	*Q&A*
4:05 – 4:25	**Modulation of Ganglioside Catabolism Using Pharmacological Chaperones: A Novel Therapeutic Approach for Alzheimer's Disease** Brandon Wustman, PhD, Amicus Therapeutics, Inc.
4:25 – 4:35	*Q&A*
4:35 – 4:55	**Heat Shock Protein 90 in Neurodegenerative Diseases** Gabriela Chiosis, PhD, Memorial Sloan Kettering Cancer Center
4:55 – 5:05	*Q&A*
5:05 – 5:10	**Closing Remarks** Diana Shineman, PhD, Alzheimer's Drug Discovery Foundation
5:10 – 7:00	**NETWORKING RECEPTION & POSTER SESSION**

Tuesday, September 27	
8:00 – 8:30 am	**Continental Breakfast**
8:30 – 9:10	**PLENARY: Enhancing CNS Uptake of Biologics through Molecular Engineering** Ryan J. Watts, PhD, Genentech
III. Neuroprotection and Synaptic Enhancement Chair: Howard Fillit, MD, Alzheimer's Drug Discovery Foundation	
9:10 – 9:15	**Session Overview** – Howard Fillit, MD, Alzheimer's Drug Discovery Foundation
9:15 – 9:35	**Tricyclic Pyrone Compounds and Axonal Trafficking Dysfunction in AD** Eugenia Trushina, PhD, Mayo Clinic College of Medicine
9:35 – 9:45	*Q&A*
9:45 – 10:05	**Targeting Neuronal Calcium Signaling to Halt AD-linked Synaptic Dysfunction** Grace E. Stutzmann, PhD, Rosalind Franklin University School of Medicine
10:05 – 10:15	*Q&A*
10:15 – 10:35	**Klotho Enhances Oligodendrocyte Maturation and Myelination** Carmela R. Abraham, PhD, Boston University School of Medicine
10:35 – 10:45	*Q&A*
10:45 – 11:15	**BREAK**
11:15 – 11:35	**Mapping the Binding Site of HDAC 2 for the Design of Novel HDAC Inhibitors Lacking Zinc Binding Group** Pavel A. Petukhov, PhD, University of Illinois at Chicago
11:35 – 11:45	*Q&A*
11:45 am– 12:05 pm	**Targeting the Neuronal Calcium Sensor (NCS) Protein, VILIP-1, for Cognitive Impairment in CNS Disorders** Karl-Heinz Braunewell, PhD, Southern Research Institute
12:05 – 12:15	*Q&A*
12:15 – 12:35	**Efficacy of Herbal Extract, Tetramethylpyrazine, for Alzheimer's Disease** Zhiqun Tan, MD, PhD, University of California, Irvine
12:35 – 12:45	*Q&A*
12:45 – 1:45	**LUNCH & POSTER SESSION**
IV. Accelerating Clinical Trials for Alzheimer's Disease through Biomarkers Chair: Tim West, PhD, C2N Diagnostics	
1:45 - 1:50	**Session Overview** – Tim West, PhD, C2N Diagnostics, Inc.
1:50 – 2:10	**A Novel Application of Stable Isotope Labeling for Disease Detection and Clinical Trials in Alzheimer's** Tim West, PhD, C2N Diagnostics
2:10 – 2:20	*Q&A*
2:20 – 2:40	**TOMM40 Genetic Biomarker: Accelerating Drug Development for Alzheimer's Disease and Frontotemporal Dementia** Allen D. Roses, MD, FRCP (hon.), Duke University
2:40 – 2:50	*Q&A*
2:50 – 3:10	**CSF Biomarkers of FTLD-TDP and FTLD-Tau: A Multi-Center Study** William Hu, MD, PhD, Emory University School of Medicine
3:10 – 3:20	*Q&A*
3:20 – 3:50	**BREAK**
3:50 – 4:10	**Use of Targeted Multiplex Proteomic Strategies to Identify Plasma and Cerebral Spinal Fluid-Based Biomarkers in Alzheimer's Disease** Judith Siuciak, PhD, The Biomarkers Consortium, Foundation for the National Institutes of Health
4:10 – 4:20	*Q&A*
4:20 – 4:40	**Pilot Trial of Metformin in the Prevention of Alzheimer's Disease** José A. Luchsinger, MD, MPH, Columbia University
4:40 – 4:50	*Q&A*
4:50 – 5:00	**Closing Remarks** Howard Fillit, MD, Alzheimer's Drug Discovery Foundation

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AFTD The Association for Frontotemporal Dementias

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BioNJ Advancing the State of Biotechnology

HealthCare Institute of New Jersey

Lewy Body Dementia Association, Inc.

AFTD The Association for Frontotemporal Degeneration

2011 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 2011 Young Investigator Scholars are:

Robin Barry Chan, PhD, *Columbia University*

Yi-Fang Chuang, MD, *Johns Hopkins Bloomberg School of Public Health*

Paige Elizabeth Cramer, BS, *Case Western Reserve University*

Kieren JM Egan, BS, *University of Edinburgh*

Akina Hoshino, BA, *University of Maryland-Baltimore*

Ali Jawaid, MD, *University Hospital Zurich*

Serene Keilani, PhD, *Mount Sinai School of Medicine*

Christopher Stephen Lewis, BS, *University of Oklahoma*

Tao Ma, MD, PhD, *New York University*

Carolina Andrea Oliva, PhD, *Center for Aging and Regeneration CARE & Pontificia Universidad Católica de Chile*

Marguerite Prior, PhD, *Salk Institute for Biological Studies*

Naoki Tajiri, PhD, *University of South Florida College of Medicine*

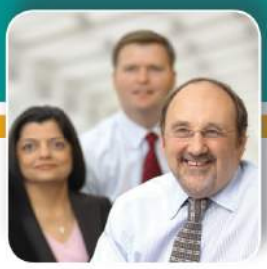
Michael J. Van Kanegan, PhD, *Duke University Medical Center*

Jason V. Wallach, BS, *University of the Sciences*

Kyle C. Wilcox, PhD, *Northwestern University*

Jiaqi Yao, MD, PhD, *Weill Cornell Medical College*

Daria Zamolodchikov, BA, *The Rockefeller University*

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– David Nicholson, PhD, Senior Vice President and Head
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OPPORTUNITIES FOR FUNDING

PROGRAM TO ACCELERATE CLINICAL TRIALS (PACT)

The Alzheimer's Drug Discovery Foundation (ADDF) has created the Program to Accelerate Clinical Trials (PACT) to increase the number of innovative drugs tested in humans at the crucial proof-of-concept stage for Alzheimer's disease. This program will primarily fund biomarker outcome-based, Phase IIa pilot clinical trials for Alzheimer's disease, although other clinical applications may also be considered.

THE ADDF/BELFER APOE THERAPEUTICS INNOVATION PROGRAM

The Alzheimer's Drug Discovery Foundation (ADDF) and the Robert A. and Renée E. Belfer Family Foundation established The ADDF/Belfer ApoE Therapeutics Innovation Program to accelerate the development of novel therapeutics specifically designed to target apoE pathological mechanisms. This program will support both preclinical and clinical stage programs.

GENERAL REQUEST FOR PROPOALS

The ADDF General RFP funds drug discovery and development research programs in the field of Alzheimer's disease, related dementias and cognitive aging in academic centers and biotechnology companies worldwide. The ADDF does not support basic research and solely allocate funding towards translational research efforts.

QUARTERLY DEADLINES FOR ALL PROGRAMS

For more information or to apply for funding, please visit:
www.alzdiscovery.org/index.php/research-programs/grant-opportunities

For program related inquiries, please contact:

Diana Shineman, PhD
Assistant Director, Scientific Affairs
Phone: 212-901-8007
dshineman@alzdiscovery.org

For application inquiries, please contact:

Niyati Thakker
Grants Assistant
Phone: 212-901-8019
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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

Daniel M. Skovronsky, MD, PhD, Avid Radiopharmaceuticals, Inc., a wholly-owned subsidiary of Eli Lilly and Company

Dr. Skovronsky, President and CEO of Avid, founded the company and began operations in mid-2005. Over the last six years, Dr. Skovronsky has led clinical programs in Alzheimer's, Parkinson's and Diabetes at Avid. Under Dr. Skovronsky's leadership, Avid raised $70M in venture capital financing to support this research. Dr. Skovronsky has more than 40 publications in the field and has served as principle investigator on numerous NIH research grants. Dr. Skovronsky trained as a resident in Pathology and completed a fellowship in Neuropathology at the Hospital of the University of Pennsylvania. Dr. Skovronsky received his MD and PhD from the University of Pennsylvania and did his undergraduate training in molecular biochemistry at Yale University.

Dr. Skovronsky was named by the Philadelphia Business Journal as one of their "Forty under Forty" business leaders in the region in 2006, by PharmaVoice magazine as one of the 100 top pharmaceutical business leaders in 2007, by Ernst & Young as the Entrepreneur of the Year in the Greater Philadelphia Region in 2009 and Life Sciences CEO of the Year by the Philadelphia Business Journal in 2010. Avid was named the Life Sciences Startup Company of the Year in 2007 by the Eastern Technology Council, received the 2007 Frost & Sullivan Molecular Imaging Technology Innovation of the Year award and was named Best Incubator Company and Best Local-Based-Research Company in 2010 by the Philadelphia Business Journal. Avid's lead product candidate, Florbetapir (AV-45), was recently named the #1 Innovation of 2011 by the Cleveland Clinic. Avid was acquired by Eli Lilly & Company in December of 2010 for up to $800 million and now operates as a wholly owned subsidiary of Eli Lilly.

From Academic Discovery Towards an FDA Approval for a Novel Amyloid Imaging Agent

Daniel M. Skovronsky

Avid Radiopharmaceuticals, Inc., a wholly-owned subsidiary of Eli Lilly and Company, Philadelphia, PA

Florbetapir F 18 has been studied in Phase I, Phase II and Phase III clinical trials to support development as a brain amyloid plaque imaging agent. Phase I studies determined the safety profile, radiation dosimetry and test-retest reliability of the compound in healthy controls and Alzheimer's disease (AD) patients. Phase II studies focused on cross-sectional studies of AD subjects, mild cognitive impairment (MCI) subjects and cognitively normal controls of various ages. The Phase III study compared in vivo imaging outcomes with neuropathological measures of amyloid pathology at autopsy, and showed a significant correlation between tracer retention in the brain in vivo and amyloid pathology subsequently measured at autopsy. In addition to these completed Phase I – III registration studies, florbetapir F 18 is also being used in several large ongoing longitudinal studies. Interim results from these studies will be presented, including an analysis of the prognostic value of amyloid burden measured by florbetapir-PET, measurements of longitudinal changes in amyloid burden by florbetapir-PET and correlation of florbetapir-PET with other biomarkers for Alzheimer's disease (including 11C-PiB and CSF Abeta).

I. Targeting Tau for Alzheimer’s Disease and Related Dementias
Chair: Illana Gozes, PhD, Allon Therapeutics Inc.

The Discovery and Preclinical Progress of the Neuroprotective Peptide, davunetide, in the Treatment of Tauopathies
Illana Gozes, PhD, Allon Therapeutics Inc.

Modulating the Hsp70/DnaJ Protein Interface to Dictate Triage Decisions for Tau
Chad Dickey, PhD, University of South Florida

Developing a Tau Imaging Agent for Alzheimer’s Disease
Jeff Kuret, PhD, Ohio State University

Targeting Tau Oligomers through Immunotherapy
Rakez Kayed, PhD, University of Texas Medical Branch

Tau Clearance by Autophagy
Karen Duff, PhD, Columbia University

Illana Gozes, PhD, Allon Therapeutics Inc.

Dr. Gozes is a Professor of Clinical Biochemistry, the Lily and Avraham Gildor Chair for the Investigation of Growth factors at Tel Aviv University (TAU) Sackler Faculty of Medicine, where she heads the Dr. Diana and Zelman Elton (Elbaum) Laboratory for Molecular Neuroendocrinology. Professor Gozes serves as the Director of the Adams Super Center for Brain Studies at Tel Aviv University and the Levie-Edersheim-Gitter Institute for Functional Brain Imaging, a collaborative project between Tel Aviv University and the Sourasky Medical Center. Professor Gozes serves or has served as a member (or chair) of several faculty/university/national and international committees including serving now as a member of the Board of Governors of Tel Aviv University, the Tel Aviv University Senate, the Scientific Review Board of the Alzheimer's Drug Discovery Foundation (New York, USA), the Scientific Review Board of the Rett Foundation, member of several Editorial Boards (Peptides, American Journal of Alzheimer's Research and other Dementias, Peptides Research and Therapeutics, Pharmaceutical Drug Design) and Past President of the Israel Society for Neuroscience. Professor Gozes is the Editor-in-Chief of the Journal of Molecular Neuroscience, the Secretary General of the European Neuropeptide Club and the Chair of the Summer Neuropeptide Conference, The International Advisory Committee of VIP PACAP and Related Peptides and Chair of the 2011 Conference.

Dr. Gozes is the scientific founder, Chief Scientific Officer of Allon Therapeutics, where she serves as a member of the Board of Directors. Allon was chosen as the "Most Innovative Development Company" in the New Economy 2010 Pharmaceutical & Healthcare Awards sponsored by New Economy Magazine and won the 2011 Gold Leaf Award as the Early Stage Company of the Year (Health) from BIOTECanada. Prof. Gozes has published extensively in the fields of molecular neuroscience and neuroprotection (over 230 publications as cited PUBMED; over 280 including a book, book chapters and reviews). She is co-inventor of more than 15 patents and applications (with more than 125 results found in the Worldwide data base for Gozes as an applicant or inventor, including the composition of matter patent on davunetide, Allon's lead compound.) Professor Gozes mentored more than 50 students toward successful MSc and PhD degrees.

Professor Gozes received a BSc from Tel Aviv University, a PhD from The Weizmann Institute of Science, was a Weizmann Postdoctoral Fellow at Massachusetts Institute of Technology, Research Associate/Visiting Scientist at the Salk Institute and the Scripps Clinic and Research Foundation, a Senior Scientist/Associate Professor at the Weizmann Institute and a distinguished Fogarty-Scholar-in-Residence at the National Institutes of Health (USA).

The Discovery and Preclinical Progress of the Neuroprotective Peptide, *davunetide*, in the Treatment of Tauopathies

Illana Gozes*, Anat Idan-Feldman, Yan Jouroukhin

The Adams Super Center for Brain Studies; The Lily and Avraham Gildor Chair for the Investigation of Growth Factors; Department of Human Molecular Genetics and Biochemistry, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
**Allon Therapeutics Inc., Vancouver, BC, Canada*

Davunetide (NAP=NAPVSIPQ), a peptide derived from activity-dependent neuroprotective protein (ADNP), is a neuroprotective drug candidate (CNS Drug Rev. 2005; 11:353). ADNP and activity-dependent neurotrophic factor (ADNF) are potent neuroprotective proteins secreted from glial cells in response to vasoactive intestinal peptide (VIP) stimulation that protect neurons against death induced by electrical blockade. ADNF was biochemically isolated (size and charge fractionations) from glial VIP-conditioned medium and NAP (davunetide) was discovered by structural-functional similarity to a similar moiety within ADNF (J Mol Neurosci. 2000 14:61). Assessment of NAP (davunetide) and all D-amino acid ADNF-9 (SALLRSIPA) neuroprotection in primary cortical neuro-glial cultures treated with amyloid beta showed that

both peptides reduced toxin-related neuronal damage and tau hyperphosphorylation (Curr Pharm Des. 2011 Jul 5. [Epub ahead of print]). Studies in neuron-enriched cultures subjected to ischemia suggested that the effects on tau hyperphosphorylation were coupled to caspase 3 activation. Studies in a rat model of cognitive impairment associated with diabetes showed in vivo protection against glial apoptosis coupled with synaptic protection (synaptophysin). Furthermore, T2 magnetic resonance imaging revealed atrophy in the prefrontal cortex of the diabetes rat group, which was prevented by davunetide (NAP) treatment and paralleled protection against impairment of spatial memory (Neurobiology of Disease, 2011, in press). Further, in a model of amyotrophic lateral sclerosis, davunetide (NAP) treatment protected against brain damage as detected by T2 and diffusion tensor imaging (DTI). Davunetide is currently being tested in a Phase II/III clinical trial assessing safety and efficacy in patients with progressive supranuclear palsy (Allon Therapeutics Inc., Trial identifier NCT01110720), a sporadic neurodegenerative disorder characterized by extensive tau pathology.

Support: Allon Therapeutics Inc., AMN Foundation, CFTAU/Montreal Circle of Friends.

Chad Dickey, PhD, University of South Florida

Dr. Chad Dickey joined the faculty at the Byrd Alzheimer's Institute in September 2008. Dr. Dickey earned his PhD from the University of South Florida under the direction of Dr. David Morgan in 2004. His post-doctoral training was done at the Mayo Clinic in Jacksonville under the direction of Dr. Michael Hutton, an expert in the field of Alzheimer's disease genetics. He was a recipient of a New Investigator Award from the Alzheimer's Association and a Rosalinde and Arthur Gilbert Foundation/AFAR New Investigator Award in Alzheimer's Disease. Dr. Dickey has conducted two research projects for the Society for Progressive Supranuclear Palsy to study the mechanisms behind this particular form of hereditary dementia. He is currently funded through the NIH, the Alzheimer's Association, the Alzheimer's Drug Discovery Foundation and CurePSP for his research related to molecular mechanisms of Alzheimer's disease and tauopathies.

Modulating the Hsp70/DnaJ Protein Interface to Dictate Triage Decisions for Tau

Jose F. Abisambra, Umesh K. Jinwal, Chad A. Dickey

University of South Florida, Tampa, FL

Accumulation of the microtubule associated protein tau inflicts neuronal death and memory loss associated with Alzheimer's disease (AD). Tau also accumulates in more than 15 other neurodegenerative diseases collectively termed tauopathies. Therefore tau is a tractable therapeutic target for AD and many other disorders. The chaperone family of proteins, and in particular the heat shock protein 70 (Hsp70) family, is critical for tau processing. Indeed, the major cytosolic variant of the Hsp70 family, Hsp73, is strongly associated with granulovacular degenerating bodies (GVDs), which are major tau-associated pathological entities in AD neurons that are linked to autophagic clearance mechanisms. Co-localization studies have also shown that Hsp70 associates with accumulated tau in the brain. However, the actual mechanisms involving Hsp70 with tau biology have been challenging to define. It has been shown that Hsp70 can either promote tau clearance or functionally preserve it. The reason for this dichotomy, however, is finally becoming clear. Hsp70 acts to seek out, identify and hold onto tau, but other chaperones termed DnaJ proteins by manipulating substrate selection and Hsp70 ATPase activity dictate whether this Hsp70 bound tau should be preserved, sequestered or destroyed. Thus, new evidence is emerging that will define the most therapeutically relevant chaperone targets for the treatment of AD.

Jeff Kuret, PhD, Ohio State University

Dr. Kuret is a Professor of Molecular and Cellular Biochemistry at The Ohio State University. He completed his BS degree in biochemistry at the University of California, Los Angeles, and conducted graduate work with Professor Howard Schulman at Stanford University. After earning his PhD degree in Pharmacology, he joined the laboratory of Sir Philip Cohen in the Medical Sciences Institute, Dundee, Scotland as a postdoctoral fellow, and served on the faculties of Cold Spring Harbor Laboratory and Northwestern University. He currently serves on the Drug Discovery (MNPS-C) review panel at the NIH Center for Scientific Review, and on the editorial boards of the Journal of Biological Chemistry and Current Alzheimer Research. Dr. Kuret's laboratory focuses primarily on tau aggregation and neurofibrillary lesion formation in Alzheimer's disease and frontotemporal lobar degeneration.

Developing a Tau Imaging Agent for Alzheimer's Disease

Jeff Kuret

The Ohio State University College of Medicine, Columbus, OH

Current methods for whole-brain imaging of dementia patients capture the binding of radiolabeled compounds to aggregated forms of the β-amyloid (Aβ) peptide. Development of selective radiotracers for tau-bearing neurofibrillary lesions could complement the established Aβ imaging signature in several ways. First, neurofibrillary lesions appear at certain sites of predilection decades before the onset of dementia, potentially providing the means to detect disease at very early stages. Second, unlike Aβ aggregates, tau aggregate load correlates with neurodegeneration and cognitive decline in AD, providing a potential surrogate marker for disease. Because of the well-established relationship between disease progression and spatial distribution of neurofibrillary pathology, tau-based imaging could help monitor the effectiveness of drug treatments over time. Finally, neurofibrillary lesions are found in chronic traumatic encephalopathy and certain forms of frontotemporal lobar degeneration. Thus tau-based imaging agents also may aid the diagnosis of dementing illnesses that are difficult to distinguish based solely on clinical presentation and that lack Aβ lesions. Here I will summarize our progress in developing tau-based imaging agents. First, using pharmacokinetic modeling methods, I will describe the molecular properties needed for detection of neurofibrillary lesions in the presence of competing aggregates such as amyloid plaques. Second, using biochemical methods, I will describe the interactions between small molecules and cross-β-sheet aggregates, and the role of amino acid side chains in imparting binding selectivity. Finally, through pharmacological analysis, I will assess the feasibility of identifying probes with selectivity for tau relative to Aβ.

Rakez Kayed, PhD, University of Texas Medical Branch

Assistant Professor at the Departments of Neurology and Cell Biology and Neuroscience, and a member of George & Cynthia Mitchell Center for Neurodegenerative Diseases at University of Texas Medical Branch, Galveston, TX.

Dr. Kayed is a pioneer in the development of conformational antibodies and their applications, and has coauthored more than sixty articles in peer-reviewed journals.

Dr. Kayed`s research focuses on tau and amyloid oligomers in neurodegenerative disorders, their structure, toxicity and role in the disease pathogenesis. We were able to engineer conformation specific mouse monoclonal antibodies against tau and amyloid oligomers. The antibodies we developed do not recognize endogenous functional proteins e.g. monomeric tau; they specifically bind and eliminate the pathological oligomeric form of the protein. We use these antibodies and other reagents and methods we developed to study neurodegenerative diseases in cell cultures, animal models and postmortem tissues.

These novel reagents have many applications, including vaccine development for treatment for AD and other tauopathies, early diagnosis and biomarkers, drug discovery and the design of new reagents that can decrease or eliminate tau and amyloid neurotoxicity.

Targeting Tau Oligomers through Immunotherapy

Rakez Kayed

University of Texas Medical Branch, Galveston, TX

Tau oligomers represent a neurotoxic entity that forms prior to NFTs and has emerged as the true pathogenic tau species in neurodegenerative tauopathies and a possible mediator of amyloid-β (Aβ) toxicity in AD. Recent findings from animal models of tauopathies suggest that tau oligomers play a key role in eliciting behavioral impairments. We developed a novel anti-tau oligomer specific antibody (TOMA). This antibody does not recognize the soluble functional tau or mature tau tangles and has a high affinity to tau oligomers. We used TOMA to vaccinate two animal models the (JNPL3) overexpressing mutant human tau protein P301L and the Tg2576 overexpressing human APP with the Swedish mutation, in both models single TOMA injection reversed the phenotypes. Biochemical and immunohistological analyses revealed that the improvement coincides with reduction of tau oligomers not NFTs or phospho-tau species in the P301L tau model. In the Tg2576 model the improvement coincides with the reduction of both tau and Aβ oligomers without affecting the plaques load, this novel finding indicate that the relation between Aβ and tau is more complex than previously depicted.

Karen Duff, PhD, Columbia University and New York State Psychiatric Institute

Dr. Duff received her PhD from Sydney Brenner's department at the University of Cambridge (UK) in 1991. From 1991-92 she undertook a post-doc position in London with Alison Goate, then from 1992-1994 with John Hardy at USF Tampa, FL where she held an assistant professor position from 1994-96. From 1996-1998 she was an associate professor at Mayo Clinic, Jacksonville, FL. From 1998-2006 she held an associate professor position, at the Nathan Kline Institute/ New York University, New York. Since 2006 she has been a tenured professor at the Taub Institute at Columbia University, with a joint position at the New York State Psychiatric Institute where she continues her translational research program. She has been awarded several honors and awards including the Potamkin Prize in 2006.

In the last 20 years, Dr. Duff has genetically engineered mouse models for AD, tauopathies and synucleinopathies. These mice have been used in a wide range of studies from MRI and PET for diagnostics development, to proof-of-concept testing of therapeutic targets. Currently, her main interest is in studying how AD related pathology and dysfunction propagates though the brain, the role of aging and ApoE genotype in AD and the role of autophagy in tauopathies. Dr. Duff's CV includes over 110 peer reviewed research articles and she is a regular speaker at scientific meetings around the world. Her work is mainly funded by the NIH.

Tau Clearance by Autophagy

Karen Duff, Natura Myeku, Wai-Haung (Ho) Yu

Columbia University, New York, NY

Accumulation of abnormal protein aggregates is a hall mark of multiple neurodegenerative disorders including Alzheimer's disease (AD), frontotemporal lobe dementia (FTD) and Parkinson's disease (PD). Several approaches have been proposed to reduce the levels of abnormal proteins in cells, including modulation of protein degradation. Multiple protein degradation pathways exist including ubiquitin-proteasome system (UPS) mediated clearance which acts on smaller, misfolded proteins, and autophagy (macroautophagy, microautophagy, and chaperone mediated autophagy) which acts on larger, misfolded or aggregated proteins, and dysfunctional organelles. Controlled autophagy plays a crucial role in cell survival and in regulating multiple cell functions but loss of control has been implicated in pathogenesis of neurodegenerative diseases due to failed clearance of disease-associated proteins. As tau and tangles have come to be recognized as an important, perhaps even necessary therapeutic target to treat Alzheimer's disease, work has accelerated to understand how tau changes from a normal, soluble, axonal, microtubule-associated protein to a hyperphosphorylated, insoluble, cytosolic filamentous protein that has relocated in the somatodendritic compartment. Considerable efforts are now underway to reduce pathological forms of tau in the cell as the basis for therapeutic intervention. We have demonstrated that mice with progressive tauopathy show a decline in proteasome function, and an induction of autophagy at the same time as fibrillar tau aggregates start to accumulate. Therapeutic approaches to upregulate autophagy using drugs such as the disaccharide trehalose or the phenothiazine Methylene Blue and their impact on tau pathology and functional outcomes will be presented.

II. Inflammation, Chaperones and Novel Targets
Chair: D. Martin Watterson, PhD, Northwestern University

Design and Refinement of Novel Small Molecule Compounds Targeting Proinflammatory Cytokine Overproduction: A Potential Disease-Modifying Therapeutic Approach to CNS Diseases
D. Martin Watterson, PhD, Northwestern University

Optimizing New Drug Candidates for Protein Disulfide Isomerase, A Novel Target for Neurodegenerative Diseases
Donald C. Lo, PhD, Duke University Medical Center

Proof-of-Concept That Small Molecule Structure Correctors Are Capable of Abolishing the Detrimental Effects of Apolipoprotein E4 in Vitro by Inhibiting Domain Interaction
Robert W. Mahley, MD, PhD, Gladstone Institute of Neurological Disease and University of California, San Francisco

Tau Lowering Agents for the Treatment of Alzheimer's Disease
Allen Reitz, PhD, ALS Biopharma, LLC

Modulation of Ganglioside Catabolism Using Pharmacological Chaperones: A Novel Therapeutic Approach for Alzheimer's Disease
Brandon Wustman, PhD, Amicus Therapeutics, Inc.

Heat Shock Protein 90 in Neurodegenerative Diseases
Gabriela Chiosis, PhD, Memorial Sloan Kettering Cancer Center

D. Martin Watterson, PhD, Northwestern University

Daniel Martin Watterson holds the John G. Searle Endowed Chair Professorship at Northwestern University where he is a Professor in the Department of Molecular Pharmacology & Biological Chemistry at the Feinberg School of Medicine. Dr. Watterson has worked successfully with major pharmaceutical and biotech companies in diverse areas of drug discovery, participated actively in bringing new drug candidates to clinical development, served on the Board of Directors for technology companies, founded profitable commercial enterprises with success in deliverables and timelines, and assisted colleagues and various government agencies with science and technology development. At Northwestern, he has served as a Department Chair, Co-Director of the Graduate Curriculum in Drug Discovery and Chemical Biology and a University Center, and founding director of the Drug Discovery Program. The Drug Discovery Program, founded in 1996 and now a university center, provides a supportive intellectual infrastructure to assist cooperative faculty participants in moving their basic science research toward preclinical drug discovery and eventual commercial development, mainly through out-license. Earlier small molecule deliverables by Northwestern faculty in the area of CNS drug discovery range from a mature blockbuster drug marketed by a major pharmaceutical company to potential disease-modifying novel candidates with potential for multiple indications that are currently in promising clinical trials.

The academic basic science research in Dr. Watterson's laboratory continues to be on the elucidation of signal transduction pathways in eukaryotic organisms, examination of their role in physiology and disease states, and leveraging of the emergent knowledge of molecular and biological mechanisms to identify new points of potential therapeutic interventions. He has published in the areas of drug discovery, signal transduction, structural biology, pharmacology and medicinal chemistry, and previously developed diagnostic and research tools as well as novel small molecule therapeutic candidates licensed to industry.

Before moving to Northwestern University, Dr. Watterson held faculty positions at The Rockefeller University, where he was an Andrew Mellon Fellow, and at Vanderbilt University Medical Center, where he was Professor of Pharmacology and Howard Hughes Investigator. His doctoral training in chemical sciences was at Emory University, followed by postdoctoral training in biochemistry and bioorganic chemistry at Duke University Medical Center where he was supported by a National Research Service Award from the National Institutes of Health.

Design and Refinement of Novel Small Molecule Compounds Targeting Proinflammatory Cytokine Overproduction: A Potential Disease-Modifying Therapeutic Approach to CNS Diseases

D.M. Watterson, Brinda Braderic, S.M.Roy, V. Tokars, W.F.Anderson, L.J. Van Eldik, C. Borlongan

Northwestern University, Chicago, IL; University of Kentucky, Lexington, KY; University of South Florida, Tampa, FL

The inflammatory response is a defense or homeostasis mechanism that responds to various stressors, including infection and injury. However, excessive or prolonged responses as well as immune system dysfunction can result in tissue injury. Pharmacological intervention can be non-selective, such as steroid use, or highly targeted, such as use of non-steroidal anti-inflammatory drugs (NSAIDs) or biological response modifiers (BRMs). The pharmacological basis of therapeutic action dictates which class of interventions is most appropriate clinically. Current FDA-approved BRM drugs are macromolecules with extended pharmacodynamic effects after periodic administration. Many of these protein drugs target proinflammatory cytokines, effector proteins whose production is up-regulated in acute and chronic disorders. Currently, extensive efforts in drug development are focused on developing small molecule modulators of cytokine production to facilitate multi-drug treatment of complex diseases and extend the intervention to other indications, such as CNS diseases. In this regard, preclinical studies and clinical findings implicate glia proinflammatory cytokine up-regulation as a contributor to pathology progression in neurodegenerative diseases such as Alzheimer's disease, and in the neurologic sequelae resulting from

acute CNS injuries such as traumatic brain injury or ischemia. Therefore, targeting the relevant glia signaling pathways involved in proinflammatory cytokine overproduction may be a viable, disease-modifying, therapeutic approach. The goal would be restoration of homeostasis by attenuating excessive cytokine production back towards basal, without pan-suppression of all glia responses, using appropriate doses and intervention time windows relevant to pathology progression.

We are using a validated drug discovery engine in which chemistry, pathobiology, and pharmacology are integrated early in a recursive effort to design and discover novel, orally bioavailable, CNS-penetrant, selective, small molecule drug candidates that attenuate excessive proinflammatory cytokine production and improve neurologic end points. One mechanism involved in cytokine overproduction by activated glia and in neuronal dysfunction is stressor-induced stimulation of protein phosphorylation cascades that converge on activation of the p38 MAPK family of protein kinases, especially p38alpha MAPK. We are testing the hypothesis that p38alpha MAPK is a key in vivo contributor to increased CNS proinflammatory cytokine production and neuronal dysfunction in response to certain disease-relevant stressors, and that inhibition of p38 MAPK signaling in the CNS can lead to improved neurologic outcomes. Structure and chemoinformatics assisted drug design started with an existing scaffold and provided a novel standard of comparison compound with in vivo function. The lead compound serves as the foundation for ongoing medicinal chemistry refinement and risk reduction activity analyses. Clearly, the p38MAPK targeted drug candidates might engage the kinase in both glia and neurons, and this dual action via a single molecular target could add to desired pharmacodynamic effects. We complemented the single molecular target approach for p38 MAPK by using a fragment expansion, phenotypic screening approach with the goal of developing novel small molecule candidates that also attenuate proinflammatory cytokine up-regulation but are NOT p38MAPK inhibitors. These have proved effective in diverse animal models of disease where proinflammatory cytokine up-regulation has been implicated in pathology progression. Candidates for clinical development with promising preclinical pharmacological profiles are among the multiple deliverables from this campaign.

Our results provide a preclinical proof of concept that inflammatory cytokine overproduction and the associated neuronal dysfunction can be attenuated by use of novel small molecules developed by targeting distinct glia signaling pathways. Deliverables from the two classes of small molecules offer a potential complement to existing and emerging therapeutic approaches to CNS disorders that are characterized by proinflammatory cytokine dysregulation as a mechanism of pathology progression.

Donald C. Lo, PhD, Duke University Medical Center

Donald Lo is an 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 10 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 latter two indications in joint ventures with Elan Pharmaceuticals. In 2002, this technology was brought back into Duke University and incorporated into the new Center for Drug Discovery (CDD) for which Lo serves as Director. The Duke CDD currently pursues multiple neurological drug discovery and development programs in collaboration with major pharmaceutical firms, biotech companies, and non-profit disease research foundations.

Optimizing New Drug Candidates for Protein Disulfide Isomerase, A Novel Target for Neurodegenerative Diseases

Donald C. Lo

Duke University Medical Center, Durham, NC

Current therapies for Alzheimer's disease (AD) provide modest symptomatic relief but none of these few FDA-approved drugs can delay or halt the progression of AD, or, critically, provide direct protection against the neuropathogenesis that is core to the disease process. In this context, there remains an urgent need to develop innovative new drug strategies that may intervene at different points in the biological pathways that underlie pathogenesis in AD.

In a multi-year collaboration with Dr. Brent Stockwell's lab at Columbia University, we have been pursuing the discovery and development of new drug candidates for neurodegenerative diseases including AD and Huntington's disease (HD). Because AD and HD are fundamentally protein misfolding diseases that very likely share core degenerative mechanisms and pathways, we have originated some screens in high-throughput HD assays that we have subsequently validated in brain slice as well as in vivo models for both HD and AD.

We describe here our recent collaborative work indicating the druggability of a newly identified cell death pathway in neurodegeneration induced by misfolded proteins such as Aβ, protein disulfide isomerase (PDI). Current studies are focused on developing second-generation lead candidate compounds targeting PDI with improved drug-like properties, blood brain barrier penetrability, and their testing and prioritization in brain slice-based assays for AD.

Robert W. Mahley, MD, PhD, Gladstone Institute of Neurological Disease and University of California, San Francisco

Dr. Robert W. Mahley is president emeritus/founder/senior investigator of The J. David Gladstone Institutes. He is an internationally known expert on heart disease, cholesterol metabolism and, more recently, Alzheimer's disease. He studies plasma lipoproteins and particularly apolipoprotein (apo) E. His seminal research has defined apoE's critical role in cholesterol homeostasis and atherosclerosis. Dr. Mahley has also made fundamental contributions to understanding the role of apoE in the nervous system, specifically in nerve injury and regeneration and in the remodeling of neurites on neuronal cells. These findings laid the groundwork for the explosion of research linking apoE4, a variant of apoE, to the pathogenesis of Alzheimer's disease and neurodegeneration. More recently, he has focused on therapeutic approaches to converting apoE4 to apoE3 both structurally and functionally and preventing the generation of apoE4 neurotoxic fragments. Dr. Mahley is also a professor of medicine and pathology at the University of California, San Francisco. He is a member of the National Academy of Sciences, the Institute of Medicine, and the American Academy of Arts & Sciences. He recently received the Builders of Science Award from Research!America for his leadership as Gladstone's founding director and president, guiding its growth to become one of the world's foremost independent research institutes.

Proof-of-Concept That Small Molecule Structure Correctors Are Capable of Abolishing the Detrimental Effects of Apolipoprotein E4 in Vitro by Inhibiting Domain Interaction

Robert W. Mahley

Gladstone Institute of Neurological Disease and University of California, San Francisco, CA

Apolipoprotein (apo) E4, the major gene and risk factor for Alzheimer's disease (AD), assumes a pathological conformation—intramolecular domain interaction. ApoE structure correctors that abolish domain interaction were identified by fluorescence resonance energy transfer (FRET) assay. Screening a ChemBridge library identified CB9032258 (a phthalazinone derivative, N-(2-hydroxy-3,5-dimethyl-phenyl)-2-(3-methyl-4-oxo-3,4-dihydro-phthalazin-1-yl)-acetamide) that reduces the FRET signal dose-dependently (IC50: 4.2 μM). Chemical modification of CB9032258 yielded well-defined structure-activity relationships (e.g., N-(4′-cyano-biphenyl-3-yl)-2-(3-methyl-4-oxo-3,4-dihydro-phthalazin-1-yl)-acetamide and 4-{4-[2-(3-methyl-4-oxo-3,4-dihydro-phthalazin-1-yl)-acetylamino]-benzyl}-piperazine-1-carboxylic acid tert-butyl ester) with enhanced FRET potencies (IC50: 23 and 116 nM, respectively). ApoE4 domain interaction is known to mediate the apoE4-specific effects of decreasing mitochondrial cytochrome c oxidase subunit 1 (~40%), reducing mitochondrial motility (~35%), and significantly inhibiting neurite outgrowth. CB9032258 and its derivatives restored these cellular functions to levels equivalent to those of apoE3. Results from the functional assays correlated well with the abilities of small molecules to block apoE4 domain interaction. Conclusion: We have established that specific phthalazinone derivatives are capable of disrupting domain interaction of newly synthesized apoE4 in the secretory pathway and reversing apoE4-specific detrimental effects on neuronal cells. These results serve as a proof-of-concept that pharmacological intervention by structural correctors can negate the detrimental effects of apoE4 and suggests a potential therapeutic approach.

Allen Reitz, PhD, ALS Biopharma, LLC

Allen Reitz, PhD, is co-founder and CEO of ALS Biopharma, LLC (www.alsbiopharma.com), based at the Pennsylvania Biotechnology Center in Doylestown, PA. He received a PhD in Chemistry from the University of California, San Diego and was at Johnson & Johnson for nearly 26 years at the Spring House, Pennsylvania facility, primarily in the area of CNS research including neurology and Alzheimer's disease. He is inventor of 46 issued U.S. patents resulting in seven compounds that have entered human clinical trials, has greater than 130 publications in peer-reviewed scientific journals, and is Editor of the journal Current Topics in Medicinal Chemistry. His research interests include early drug discovery with a core competency in medicinal chemistry.

Tau Lowering Agents for the Treatment of Alzheimer's Disease

Allen Reitz

ALS Biopharma, LLC, Doylestown, PA

The structural protein tau is implicated in the pathology of Alzheimer's disease. The heat shock response is upregulated upon physiological and oxidative stress, and one of the key heat shock proteins implicated in this process is Hsp70. Hsp70 helps to promote the refolding of misfolded proteins. Of particular relevance to Alzheimer's disease, tau is a client protein for Hsp70 and up-regulation of Hsp70 causes a decrease in tau levels. Agents that penetrate into the brain and lower tau, by any mechanism, have the potential to provide disease-modifying therapeutic relief for patients suffering from Alzheimer's disease.

We have performed a series of screening studies using a drug-like, chemically-diverse library, to understand the relation of structure to function for the following effects:

- inhibition of Hsp90,
- up-regulation of Hsp70, and
- down-regulation of tau.

We have identified compounds that are individually active in all of these assays. Of particular note, we have identified small molecule hits that lower tau levels in cell culture. We have conducted medicinal chemistry to understand the structural determinants of this biological effect, and are seeking to obtain brain-penetrant, metabolically-stable analogs that lower tau as probes to determine how such activity alters behavior in these models. If this approach is further validated in early drug discovery research, then one or more of the compounds we discover may prove to be useful as therapeutics to treat Alzheimer's disease.

Brandon Wustman, PhD, Amicus Therapeutics, Inc.

Brandon Wustman, PhD, heads the Preclinical Biology department at Amicus Therapeutics, Inc. and specializes in the development of pharmacological chaperones for the treatment of diseases associated with the misfolding and mistrafficking of proteins. Dr. Wustman received his PhD in biology from Michigan Technological University in 1998 and was awarded a postdoctoral fellowship from the Alexander Von Humboldt Society where he continued his research on protein folding and trafficking at the University of Cologne in Cologne, Germany. In 2000, Dr. Wustman joined Dr. John Evan's laboratory in the chemistry department at New York University to study protein folding at the molecular level using a combination of NMR spectroscopy, MALDI/TOF and molecular modeling techniques.

Since joining Amicus in 2002, he has applied a wide variety of analytical, biochemical and cell biological techniques to 1) better understand the cellular pathologies of various lysosomal storage disorders and their relationship to other more common neurodegenerative disorders and 2) to study the effects of pharmacological chaperones on protein folding, trafficking and cellular stress pathways. His labs' drug discovery efforts and mechanism-of-action studies have contributed to the development of three therapies that entered clinical trials as potential treatments for Fabry (Phase 3), Gaucher (Phase 2) and Pompe (Phase 2) diseases. Additionally, his lab has been exploring how impaired glycosphingolipid/ganglioside metabolism may contribute to neurodegeneration and developing pharmacological chaperones that can modulate lipid metabolism as a approach to treating neurodegenerative diseases such as Parkinson's and Alzheimer's. We have identified several animal models with impaired glycosphingolipid catabolism that develop PD- and AD-like pathologies and some of these animals are being used to study the links between glycosphingolipid metabolism disorders and various neurodegenerative diseases (e.g., Gaucher and Parkinson's diseases) and to examine the effectiveness of pharmacological chaperone treatment. In 2006, his team received a "Therapeutics Initiative Grant" from the Michael J. Fox Foundation to further investigate the use of chaperones for the treatment of Parkinson's disease and now several molecules are in advanced preclinical development for PD. In 2010, he received a grant from the Alzheimer's Drug Discovery Foundation which is focused on demonstrating in vivo proof-of-concept for increasing ganglioside catabolism as a potential therapy for Alzheimer's disease. Additionally, his team is currently developing presenilin-targeted pharmacological chaperones for the treatment of early onset familial Alzheimer's disease.

Modulation of Ganglioside Catabolism Using Pharmacological Chaperones: A Novel Therapeutic Approach for Alzheimer's Disease

Brandon A. Wustman[1], Sam Gandy[2]

[1]Amicus Therapeutics, Inc., La Jolla, CA; [2]Mount Sinai School of Medicine New York, NY

Many neurodegenerative disorders are characterized by the accumulation and aggregation of amyloid-β peptide (Aβ), hyperphosphorylated tau, and α-synuclein. Mounting evidence points to a deficient lysosomal system as a central cause of these disorders, supported by the genetic link between Parkinson's disease and the lysosomal storage disorder (LSD) Gaucher disease. As a result, we have investigated possible links between other LSDs and neurodegenerative disorders (e.g., Alzheimer's disease). Since intraneuronal Aβ accumulation has been observed in a mouse model of Sandhoff disease and gangliosides have been shown to promote Aβ oligomerization in vitro, we analyzed post-mortem human brains (cortex and hippocampus) from individuals with GM1 and GM2 gangliosidoses (GM1 gangliosidosis, Tay-Sachs disease, and Sandoff disease; n = 8), Alzheimer's disease (AD, n=2) and age-matched controls (n=5). We observed obvious accumulation of intraneuronal Aβ, ganglioside-bound Aβ (GAβ), phospho-tau immunoreactivity, and α-synuclein in all of the gangliosidosis brains, but not in age-matched control brains. Amyloid plaques and neurofibrillary tangles were observed in the AD brains as expected. GAβ has been proposed to act as a nucleation seed for Aβ oligomerization, and is thus thought to represent a pre-fibrillar aggregate in AD.

Our preliminary studies also suggest that modulating ganglioside metabolism can alter APP metabolism, providing a novel means by which to decrease Aβ generation and increase sAPPα shedding without directly inhibiting γ- or β-secretase activity. We have previously shown that small molecules can be used to selectively stabilize and increase enzymatic activity of endogenous wild-type lysosomal hydrolases. Thus, we believe this research may lead to the development of new, disease-modifying therapies for Alzheimer's disease, as well as the rarer LSDs (e.g., Sandhoff, Tay-Sachs) that share a common pharmaceutical protein target.

Gabriela Chiosis, PhD, Memorial Sloan Kettering Cancer Center

Dr. Gabriela Chiosis is a Principal Investigator and an Associate Member in the Program in Molecular Pharmacology and Chemistry at Sloan-Kettering Institute, and an Associate Attending in the Department of Medicine of Memorial Hospital for Cancer & Allied Diseases, New York. She is also a faculty in several biomedical graduate programs such as the Program in Pharmacology, Weill Graduate School of Medical Sciences, Cornell University, the Tri-Institutional Training Program in Chemical Biology, Sloan-Kettering Institute for Cancer Center, Cornell University and The Rockefeller University and the Cancer Biology Program of the Gerstner Sloan-Kettering Graduate School. She received her graduate training at Columbia University in New York and has joined Memorial Sloan-Kettering Cancer Center in 1998. The Chiosis Laboratory investigates the significance of modulating molecular chaperones in disease treatment. In this respect, it has developed pharmacological tools instrumental in defining the roles of Hsp90 in regulating the stability and function of aberrant protein driving the neurodegenerative phenotype in tauopathies. Hsp90 inhibitors discovered by the lab are the platform for the development of several purine-scaffold Hsp90 inhibitors currently in clinical evaluation in patients with advanced cancers.

Heat Shock Protein 90 in Neurodegenerative Diseases

Gabriela Chiosis

Memorial Sloan Kettering Cancer Center, New York, NY

Hsp90 is a molecular chaperone with important roles in regulating pathogenic transformation. In addition to its well-characterized functions in malignancy, recent evidence from several laboratories suggests a role for Hsp90 in maintaining the functional stability of neuronal proteins of aberrant capacity, whether mutated or over-activated, allowing and sustaining the accumulation of toxic aggregates. This talk will summarize our current knowledge on Hsp90 in neurodegeneration and will discuss the mechanisms behind selective targeting by small molecule Hsp90 inhibitors of “pathogenic” Hsp90 species, such as characteristic of cancer cells and of neurons undergoing the neurodegenerative transformation.

CLOSING REMARKS
Diana Shineman, PhD, Alzheimer's Drug Discovery Foundation

Diana Shineman, PhD, is Assistant Director, Scientific Affairs at the Alzheimer's Drug Discovery Foundation, where she is responsible for developing and managing all aspects of the Foundation's drug discovery research programs. Dr. Shineman earned her PhD in Cell and Molecular Biology from the University of Pennsylvania (Penn). At Penn's renowned Center for Neurodegenerative Disease Research led by Drs. Virginia Lee and John Trojanowski, she studied signal transduction pathways that alter amyloid generation in Alzheimer's disease. Dr. Shineman also worked with the Center's Drug Discovery Group to perform high-throughput screening using cell-based assays. In addition to her dissertation research, Dr. Shineman was as an Editorial Intern for the Journal of Clinical Investigation and was an active member of the Penn Biotechnology Group. Dr. Shineman received a BA in Biology with a Nutrition concentration from Cornell University, where she was named a Howard Hughes Undergraduate Research Scholar. She is also a member of the Society for Neuroscience and an author on numerous peer-reviewed publications.

Dr. Shineman will present a poster at this meeting on *Accelerating Drug Discovery for Alzheimer's Disease: Best Practices for Preclinical Animal Studies.* An abstract is included in the Poster Presentation handout.

PLENARY SPEAKER
Ryan J. Watts, PhD, Genentech

Dr. Ryan J. Watts is an Associate Director and Head of the Neurodegeneration Labs at Genentech. He received his PhD from Stanford University studying nervous system development. Dr. Watts joined Genentech in 2004 to develop therapies targeting vascular biology, and more recently initiated research programs on neurodegeneration and the bloodbrain barrier. Dr. Watts received his undergraduate training from the University of Utah with a BS in Biology.

Enhancing CNS Uptake of Biologics through Molecular Engineering

Ryan J. Watts

Genentech, South San Francisco, CA

Utilizing receptor-mediated transcytosis (RMT) pathways to cross the blood-brain barrier (BBB) has been explored for several decades as a mechanism to increase protein delivery to the brain. Nevertheless, many have discovered that antibodies targeting RMT pathways, particularly transferrin receptor (TfR), accumulate in CNS vasculature and fail to cross the BBB in appreciable concentrations. We have discovered that reducing the affinity of an antibody for the TfR enhances RMT of the anti-TfR antibody across the BBB into the mouse brain where it reaches therapeutically relevant concentrations. Anti-TfR antibodies that bind with high affinity to TfR remain associated with the BBB, whereas lower-affinity anti-TfR antibody variants are released from the BBB into the brain and show a broad distribution 24 hours after dosing. We designed a bispecific antibody that binds with low affinity to TfR and with high affinity to the enzyme b-secretase (BACE1), which processes amyloid precursor protein into amyloid-beta (Abeta) peptides including those associated with Alzheimer's disease. Compared to monospecific anti-BACE1 antibody, the bispecific antibody accumulated in the mouse brain and led to a greater reduction in brain Abeta after a single systemic dose. TfR-facilitated transcytosis of this bispecific antibody across the BBB may enhance its potency as an anti-BACE1 therapy for treating Alzheimer's disease.

III. Neuroprotection and Synaptic Enhancement
Chair: Howard Fillit, MD, Alzheimer's Drug Discovery Foundation

Tricyclic Pyrone Compounds and Axonal Trafficking Dysfunction in AD
Eugenia Trushina, PhD, Mayo Clinic College of Medicine

Targeting Neuronal Calcium Signaling to Halt AD-linked Synaptic Dysfunction
Grace E. Stutzmann, PhD, Rosalind Franklin University School of Medicine

Klotho Enhances Oligodendrocyte Maturation and Myelination
Carmela R. Abraham, PhD, Boston University School of Medicine

Mapping the Binding Site of HDAC 2 for the Design of Novel HDAC Inhibitors Lacking Zinc Binding Group
Pavel A. Petukhov, PhD, University of Illinois at Chicago

Targeting the Neuronal Calcium Sensor (NCS) Protein, VILIP-1, for Cognitive Impairment in CNS Disorders
Karl-Heinz Braunewell, PhD, Southern Research Institute

Efficacy of Herbal Extract, Tetramethylpyrazine, for Alzheimer’s Disease
Zhiqun Tan, MD, PhD, University of California, Irvine

Eugenia Trushina, PhD, Mayo Clinic College of Medicine

Dr. Trushina is an Assistant Professor in the Department of Neurology at the Mayo Clinic Rochester. She received her doctoral degree from Saratov State University in Russia. Dr. Trushina received her postdoctoral training at the Mayo Clinic, Rochester where she worked with Drs. C. McMurray, R. Pagano and M. McNiven. Dr. Trushina's laboratory is focused on the understanding the role that mitochondrial dysfunction plays in multiple neurodegenerative disorders including Huntington's and Alzheimer's Diseases. Her research interests involve identification of the molecular mechanisms involved in the inhibition of mitochondrial dynamics and function, testing new mitochondria-targeted therapeutic approaches, and identification of specific biomarkers useful for early diagnosis and monitoring/predicting the disease progression. In addition to her ADDF award, Dr. Trushina is a recipient of AHAF award.

Tricyclic Pyrone Compounds and Axonal Trafficking Dysfunction in AD

Eugenia Trushina

Mayo Clinic College of Medicine, Rochester, MN

Previously, we demonstrated that small molecules, tricyclic pyrones (TP), exhibit anti-amyloid properties. In particular, TP compounds prevent cell death in celular models of Alzheimer's Disease (AD) by reducing intracellular accumulation of toxic Aβ oligomers. The lead TP compound, code named CP2, has been shown to eliminate ~80% of cerebral amyloid aggregates, including nonfibrillar A oligomers and fibrillar amyloid plaques, in 5x familial AD mice following oral or intraperitoneal administration. Preliminary pharmacokinetics and toxicity studies have demonstrated that CP2 is well tolerated and has excellent blood-brain barrier permeability and oral availability. Recently, we have demonstrated that mitochondrial dynamics, morphology and function are altered in three transgenic mouse models of familial AD (APP, PS1 and APP/PS1). Moreover, our data demonstrate that nonfibrillar A oligomers were the toxic species involved in the alteration of mitochondrial dynamics early in disease progression prior to the onset of memory and neurological phenotypes. Therefore, we tested whether administration of CP2 delays the onset and slows the progression of AD in transgenic mice, and improves mitochondrial function. Our data suggest that long-term CP2 treatment (up to 12 months) (1) does not alter the development; (2) does not cause toxic side effects; (3) does not affect animal ability to breed; (4) CP2 treatment restores Mito trafficking in neurons from embryonic AD mice whose parents were treated with CP2; (5) CP2-treated AD animals demonstrate significant improvement in memory compared to the untreated littermates. Thus, application of TP compounds represents a promissing therapeutic approach in the treatment of AD.

Grace E. Stutzmann, PhD, Rosalind Franklin University School of Medicine

Grace E. Stutzmann received her PhD from the Center for Neural Science at New York University in 1999, working with Joseph E. LeDoux. Following this, she was a postdoctoral research fellow with George Aghajanian at Yale University Medical School. A second post doctoral research fellow position followed at UC Irvine, working with Ian Parker and Frank LaFerla in the Department of Neurobiology and Behavior and the Institute for Brain Aging and Dementia. Currently, she is an Assistant Professor in Neuroscience at Rosalind Franklin University / The Chicago Medical School. Her research focuses on studying early pathogenic mechanisms contributing to AD pathogenesis, and uncovering novel therapeutic strategies to prevent disease progression. Her primary techniques include live cell imaging, electrophysiology, and molecular approaches in mouse models of AD, with particular expertise in 2-photon calcium imaging and patch clamp recordings in brain slice preparations. Grace is a member of the Society for Neuroscience, The New York Academy of Sciences, and the Society of General Physiologists.

Targeting Neuronal Calcium Signaling to Halt AD-linked Synaptic Dysfunction

Grace E. Stutzmann

Rosalind Franklin University School of Medicine, North Chicago, IL

Neuronal calcium signaling is fundamental to a myriad of synaptic processes, including neurotransmission, long term plasticity, and vesicle release. Because of this, neurons dedicate substantial metabolic resources to maintain calcium homeostasis and protect network stability. In neurodegenerative diseases involving calcium disruptions, such as Alzheimer's disease (AD), alterations in calcium homeostasis have direct effects on synaptic transmission and plasticity expression, and by association, long-term memory encoding. In AD, proximal pathogenic alterations involve dysregulated ER calcium release via ryanodine receptor (RyR) and IP3R channels, and we have previously shown increased RyR-evoked calcium responses in dendrites and spines of AD mice at young ages. The downstream implications are wide-ranging, but within synaptic compartments, the RyR-mediated calcium alterations introduce shifts in membrane excitability, synaptic transmission and synaptic plasticity thresholds.

Here we present the functional implications of early calcium signaling abnormalities for synaptic transmission and plasticity in AD mouse models, and offer novel pharmacological approaches to preserve functional synaptic properties in AD mice prior to the late disease stages associated with synaptic and memory loss. Using 2-photon calcium imaging, patch clamp electrophysiology, and field potential recordings in hippocampal brain slice preparations from 6-12 week old AD and NonTg mice, we demonstrate sensitized RyR-evoked calcium responses in pre- and post-synaptic compartments of AD hippocampal neurons. Presynaptically, disrupted ER calcium alters neurotransmitter release properties and depletes vesicular stores, while postsynaptically, aberrant RyR-evoked calcium release interacts with calcium-dependent plasma membrane channels to alter membrane excitability. Manipulating RyR function revealed notable differences in synaptic plasticity between NonTg and AD mice as well. Acute RyR antagonism blocked LTP and LTD in NonTg mice, however, this same treatment converted LTP to mild LTD, and markedly enhanced LTD, in 3xTg-AD mice. Notably, chronic treatment with RyR blockers had little effect in NonTg mice, yet, this same treatment normalized calcium signaling in the AD mice back to within control conditions. This includes reversing the aberrant ER calcium responses, altered basal synaptic transmission, and impaired plasticity expression in AD mice back to patterns observed in NonTg mice. Therefore, this RyR-targeted approach to normalizing aberrant calcium signaling early in the disease process offers an optimistic therapeutic approach to preserving synaptic and cognitive function in AD.

Carmela R. Abraham, PhD, Boston University School of Medicine

Dr. Abraham was first introduced to Alzheimer's disease (AD) research in 1980. Since then she participated in numerous studies trying to understand the biology of the amyoid precursor protein (APP), including its processing and function, and its neurotoxic and synaptotoxic fragment, amyloid beta protein (Abeta). Dr. Abraham obtained her PhD in Neuroscience from Harvard University and joined Boston University School of Medicine in 1989 where she became a Professor in 1999. Dr. Abraham's laboratory studies the molecular mechanisms leading to normal brain aging and the pathological processes that culminate in AD. AD neuropathology is characterized by the accumulation of Abeta in the brain. She also works on understanding the reason patients carrying mutations that result in early onset AD accumulate more Abeta in their brains and at an earlier age that those patients who become ill at an older age. To this end she and her team study the role of APP dimerization in Abeta formation. They have supporting evidence that inhibiting APP dimerization with small molecule compounds could constitute another avenue for lowering Abeta in the brain. In the normal aging project Dr. Abraham's team utilizes the rhesus monkey as a model for understanding changes that occur in the white matter during non-pathological aging. With microarray analysis they had identified genes that play crucial roles in brain dysfunction leading to cognitive decline. An example is Klotho, a cytoprotective, anti-aging protein. Dr. Abraham found that Klotho expression is considerably decreased in the aged brains of monkeys, rats, and mice. She and her team are now working to comprehensively characterize the role of Klotho in normal aging and disease. They have also discovered recently that Klotho can induce the differentiation of oligodendrocyte precursor cells into mature, myelinating oligodendrocytes. Since the myelin in the aging white matter and AD is compromised, enhancing Klotho expression could be beneficial by inducing myelin repair in normal aging and AD.

Klotho Enhances Oligodendrocyte Maturation and Myelination

Carmela R. Abraham

Boston University School of Medicine, Boston, MA

White matter and myelin abnormalities occur during normal aging, in Alzheimer's disease and, to a larger extent, in Multiple Sclerosis. Although the mechanisms behind this deterioration of myelin in these conditions may be entirely different, repair of the damaged myelin by the oligodendrocytes is universally necessary. Here we present a connection between the anti-aging protein Klotho, oligodendrocytes and myelin.

Our group has previously shown that myelin abnormalities and loss characterize the normal aging process of the brain and that an age-associated reduction in Klotho is conserved across a wide range of species. Predominantly generated in brain and kidney, Klotho overexpression extends life span whereas loss of Klotho accelerates the development of aging-like phenotypes. While the function of Klotho in brain is unknown, loss of Klotho expression leads to cognitive deficits that are not well explained. In the present study, we found significant effects of Klotho on oligodendrocyte functions including myelination. Microarray analysis and phosphoprotein Western analysis revealed Klotho's downstream effects involve Akt and ERK signal pathways. Klotho increased primary oligodendrocytes maturation and inhibition of Akt or ERK function blocked this effect on oligodendrocytes. In vivo studies of Klotho knockout mice and their control littermates revealed that these mice have a significant reduction in major myelin protein and gene expression compared to control mice. By immunohistochemistry the total number of oligodendrocytes was significantly lower in Klotho knockout mice. However, the most striking myelin abnormalities were observed at the ultrastructural level. Klotho knockout mice exhibited significantly impaired myelination of the optic nerve and corpus callosum. In order to decipher the mechanisms by which Klotho affects oligodendrocytes, we used enrichment analysis to predict potential transcriptional factors involved in regulating Klotho-treated oligodendrocytic MO3.13 cells. These studies are expected to provide a better understanding of the functions of Klotho in myelin biology, and lead to ways to protect brain myelin against age-dependent changes.

Pavel A. Petukhov, PhD, University of Illinois at Chicago

PhD with Dr. Alexey Tkachev at Novosibirsk Institute of Organic Chemistry (1998), postdoc with Dr. John Keana at University of Oregon (1998-2000), postdoc with Dr. Alan Kozikowski at Georgetown University (2000-2003), Assistant Professor at University of Illinois at Chicago, College of Pharmacy, Department of Medicinal Chemistry and Pharmacognosy (2004-2008), Associate Professor at University of Illinois at Chicago (2008-present), Associate Faculty at Institute for Tuberculosis Research (2004 – present), Associate Professor at the Bioengineering Department, University of Illinois at Chicago (2007 - present).

Research interests: Medicinal chemistry, computer-aided drug design, chemical biology, drug discovery. Design of potent photoreactive probes for histone deacetylases (HDAC), understanding how they photocrosslink to different HDAC isoforms, and application of this knowledge to discovery of potent HDAC inhibitors with a desired HDAC isoform activity and an improved ADMET profile. Discovery of novel potent inhibitors of pantothenate synthetase and malate synthase, novel targets for non-replicating persistent tuberculosis. Design and development of novel therapeutics for neurological diseases, cancer, tuberculosis, and hepatitis B.

Mapping the Binding Site of HDAC 2 for the Design of Novel HDAC Inhibitors Lacking Zinc Binding Group

Pavel A. Petukhov, Aditya S. Vaidya, Emma Mendonca, Bhargava Karumudi, He Bai, Caleb K. Nienow, Richard van Breemen

University of Illinois at Chicago, Chicago, IL

Inhibition of HDAC2 is an attractive therapeutic avenue for neurodegenerative diseases associated with learning and memory impairment. To uncover the full potential of inhibition of HDAC2 novel safe for long-term use and isoform-selective HDAC 2 inhibitors are needed. We hypothesized that it would be possible to design HDAC2 inhibitors lacking the zinc chelating group by targeting novel adjacent to the catalytic site pockets. In this talk we will present the first step in this direction – design and synthesis of a series of potent photoreactive HDAC 2 inhibitors and their use for the Binding Ensemble Profiling with Photoaffinity Labeling (BEProFL) of HDAC2.

Karl-Heinz Braunewell, PhD, Southern Research Institute

Dr. Braunewell obtained his PhD in Biology in 1993 at the Institute for Neurobiology (Prof. M. Schachner) at the Federal Institute of Technology in Zurich, Switzerland, and received further postdoctoral research training at the Department for Neurochemistry/Molecular Biology (Prof. E.D. Gundelfinger), Leibniz-Institute for Neurobiology in Magdeburg, Germany. In 1998, Dr. Braunewell became head of the Signal Transduction Research Group at the Leibniz-Institute for Neurobiology, and he was Lecturer in Biochemistry at the Medical Faculty of the Otto-von-Guericke University Magdeburg. In 2001, Dr. Braunewell headed the Signal Transduction Research Group at the Neuroscience Research Center (NWFZ) of the Charité, Berlin and later became Assistant and Adjunct Professor for Physiology at the Johannes Müller-Institute, Medical Faculty, Charité, at Humboldt University in Berlin. Dr. Braunewell joined Southern Research in 2006, where he is currently an independent PI in the Biochemistry and Molecular Biology Department of the Drug Discovery Division. He is also a member of the faculty at the Comprehensive Neuroscience Center (CNC) at The University of Alabama at Birmingham (UAB).Throughout his research career, Dr. Braunewell has focused on molecular and cellular mechanisms underlying brain function, particularly learning and memory. His current interest focuses on the role of neuronal calcium sensors and nicotinic acetylcholine receptors in addiction, schizophrenia and Alzheimer's disease. At Southern Research, Dr. Braunewell is actively involved in drug discovery for targets in several CNS disorders including Alzheimer's disease, addiction, depression and schizophrenia.

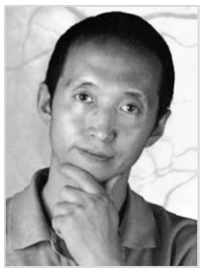
Targeting the Neuronal Calcium Sensor (NCS) Protein, VILIP-1, for Cognitive Impairment in CNS Disorders

Karl-Heinz Braunewell

Southern Research Institute, Birmingham, AL

VILIP-1 (visinin-like protein 1, gene name VSNL1) is a member of the NCS family of EF-hand calcium binding proteins, and has been implicated in Alzheimer's disease (AD). Lower expression of VILIP-1 protein and mRNA were found in hippocampus, amygdala, cingulate and temporal cortex of AD brains. The reduced expression levels correlate with neurofibrillar tangle content and the MMSE (mini mental status examination) score. Increased cerebrospinal fluid content of VILIP-1 (CSF-VILIP-1) was evaluated as a disease biomarker for AD. The most recent study in 2011 concluded that CSF VILIP-1 and VILIP-1/Aβ42 offer diagnostic utility for early AD, and can predict future cognitive impairment in cognitively normal individuals similarly to tau/Aβ42. Several lines of experimental evidence support a link between reduced expression of VILIP-1 and cognitive impairments. For instance, VILIP-1 modulates signal transduction pathways implicated in synaptic plasticity and memory, and one of its targets, the a4b2 nicotinic acetylcholine receptor, has been frequently linked to learning and memory processes as well as to cognitive decline in AD. We have used the available knowledge on VILIP-1 to design cell-based screening assays for chemical compounds modulating functional activity of VILIP-1. Our goal is to identify and develop activators of VILIP-1 function for further analysis in cognitive tests in AD animal models. Thus, VILIP-1 likely plays a role in disease mechanisms of cognitive deficits, and therefore, comprises a novel potential drug target for treatment of such cognitive impairments in neurodegenerative disorders and in the ageing population.

Zhiqun Tan, MD, PhD, University of California, Irvine



Zhiqun Tan is an Associate Research Professor in the Department of Neurology and Institute for Memory Impairments and Neurological Disorders (iMIND) at University of California Irvine School of Medicine. He received his MD (BM) in 1985 from Tongji Medical University, BSc in Biochemistry in 1987 and PhD in Biological Chemistry in 1993 from Wuhan University in China. Then he worked as a faculty member at Wuhan University in the field of environmental toxicology. 1996 he moved to the United Stated and trained as a research neuroscientist at University of Southern California Keck School of Medicine. He joined the faculty of UCI Neurology in 2002 and has been studying on neuronal degeneration with an emphasis on Alzheimer's disease. Dr. Tan's group has recently identified Alzheimer's pathological hallmarks in the retina in both Alzheimer's transgenic mice and postmortem tissues from AD patients. His research is currently focused on understanding Alzheimer's lesions in the retina as a biomarker for an assessment of the disease activity through a non-invasive imaging approach. He is also highly motivated to develop therapeutic strategies for the treatment of neurodegenerative disorders using naturopathic compounds. In this regard, his recent work has demonstrated efficacy of tetramethylpyrazine, a small molecule from chuanxiong (a traditional Chinese medicine), for both improvement of cognitive function and amelioration of pathological lesions in the brain and eye in Alzheimer's transgenic mice. He is evaluating more compounds from known herbal medicines for the potential therapeutic use for Alzheimer's and other neurodegenerative diseases.

Efficacy of Herbal Extract, Tetramethylpyrazine, for Alzheimer's Disease

Zhiqun Tan[1,2], Wayne W. Poon[2], Emily Wu[1], Scott Chen[1], Stacey Lee[1], Carl W. Cotman[1,3], Steven S. Schreiber[1,2,3,4]

[1]Departments of Neurology, [2]Anatomy and Neurobiology, and [3]Institute for Memory Impairments and Neurological Disorders, University of California Irvine School of Medicine, Irvine, CA; [4]Neurology Section, VA Long Beach Healthcare System, Long Beach, CA

For more than 2500 years herbal preparations have been widely used in traditional Chinese medicine (TCM) for the purposes of general health care and treatment of a variety of diseases. Hundreds of different herbal species with demonstrated neuroprotective efficacy have been used for the treatment of neurological disorders including dementia. Among the advantages of purified phytochemicals, which are the active components of herbs, are stability proven in the ambient environment and ability to cross the blood-brain barrier following oral administration. Therefore naturopathic compounds are becoming increasingly promising as therapeutic candidates for neural protection and the treatment of Alzheimer's disease (AD).

Tetramethylpyrazine (TMP), also called as ligustrazine, is an alkaloid originally isolated from the rhizome of the Chinese medicinal herb, *Ligusticum wallichii* Franchat (*chuanxiong*). For hundreds of years, *chuanxiong* has been used as a therapeutic for heart, kidney and brain diseases by practitioners of TCM. Experimental evidence indicates that TMP is an anti-inflammatory and anti-oxidant small molecule with the capacity to block calcium influx into cells. In this study, we tested the efficacy of TMP in two different Alzheimer's transgenic mouse models, i.e., 3xTg-AD and 5xFAD mice. The therapeutic efficacy of two compounds, i.e., chemically-synthesized TMP and herb-derived TMP, were tested in these two models. Both AD and wild type (WT) mice were fed chow containing either synthetic or natural TMP (300 mg/kg). Equivalent numbers of AD and WT littermates fed identical chow without TMP were used as controls. After 60-80 days animals were tested in a novel object recognition task (NORT) for short-term memory and the Morris water maze (MWM) for spatial learning. Mice were then euthanized and both the brain and eyes removed for histopathological and biochemical analyses. As expected, both 3xTg-AD (12~14-month old) and 5xFAD (6-month old) mice had considerable deficits in learning and memory as revealed by NORT and MWM results. In contrast, treatment with synthetic TMP, but not herb-derived TMP, significantly

improved cognitive performance in both lines of AD mice. Notably, there was a significant reduction in beta-amyloid plaques and neuroinflammatory markers in the brain and retina of mice treated with either form of TMP. Further analysis demonstrated decreased amounts of lipid peroxidation products as well as oligomeric forms of beta-amyloid in brain lysates from TMP-treated mice. We conclude that TMP reduces beta-amyloid and neuroinflammation in both the brain and retina and ameliorates cognitive dysfunction in AD mice. Moreover, our results suggest that natural preparations of phytochemicals may be less efficacious than their synthetic counterparts.

Acknowledgements: This study is supported by the Alzheimer's Drug Discovery Foundation.

IV. Accelerating Clinical Trials for Alzheimer's Disease through Biomarkers Chair: Tim West, PhD, C2N Diagnostics

A Novel Application of Stable Isotope Labeling for Disease Detection and Clinical Trials in Alzheimer's
Tim West, PhD, C2N Diagnostics

TOMM40 Genetic Biomarker: Accelerating Drug Development for Alzheimer's Disease and Frontotemporal Dementia
Allen D. Roses, FRCP (hon.), MD, Duke University

CSF Biomarkers of FTLD-TDP and FTLD-Tau: A Multi-Center Study
William Hu, MD, PhD, Emory University School of Medicine

Use of Targeted Multiplex Proteomic Strategies to Identify Plasma and Cerebral Spinal Fluid-Based Biomarkers in Alzheimer's Disease
Judith Siuciak, PhD, The Biomarkers Consortium, Foundation for the National Institutes of Health

Pilot Trial of Metformin in the Prevention of Alzheimer's Disease
José A. Luchsinger, MD, MPH, Columbia University

Tim West, PhD, C2N Diagnostics

Dr. Tim West graduated from the Washington University School of Medicine in 2006 with a PhD in Neuroscience and Molecular & Cellular Biology. His thesis work, completed in the laboratory of Dr. David Holtzman within the Department of Neurology, involved investigating the mechanisms of cell death after ischemic stroke in newborns. Following the completion of his PhD, Dr. West served as a Post-Doctoral Fellow and later Staff Scientist in Dr. Holtzman's laboratory. He also served as the Assistant Director of Technology Development for the Hope Center for Neurological Disorders. Dr. West joined C2N Diagnostics in November, 2007 as the Director of Laboratory Operations and later as the Vice President of Research and Development. During his time at C2N, Dr. West has overseen the transference of the SILK technology to the company, and implemented quality controls and systems within the company. Dr. West has also led C2N's research and development efforts in the proteomic measurement of other proteins implicated in neurodegeneration. He has served as a director to multiple clinical studies using the SILK technology. In addition, Dr. West has served as the Company's Principal Investigator on numerous grants awarded from multiple private foundation and public sources of support for funding.

A Novel Application of Stable Isotope Labeling for Disease Detection and Clinical Trials in Alzheimer's

Tim West

C2N Diagnostics, St. Louis, MO

One of the hallmarks of Alzheimer's disease (AD) is the presence of amyloid plaques in the brain. One of the main constituents of the plaques is the peptide amyloid beta. Over the last decade, research from animals and humans have pointed to plaques as a leading cause for the progression of Alzheimer's disease and research in humans have shown that amyloid plaques are most likely present in the brain long before any clinical signs of Alzheimer's disease (such as memory loss) are present. It has also become clear over the past decade that in order to develop disease modifying therapeutics that can prevent or slow down the progression of AD it is important to have the right tools for diagnosis and staging of AD in order to ensure that you are enrolling the right population in your clinical trials. Especially as the focus is shifting towards treating the early stages of the disease or disease prevention this becomes exceedingly important.

Ideally a diagnostic test for AD would be easy to administer and have high predictive value. By combining certain procedures with the C2N proprietary stable isotope labeling methods, C2N hopes to create a blood based diagnostic test that can assess the levels of plaque in the brain and may thus allow pre-clinical diagnosis of Alzheimer's disease. If this test translates to humans it will greatly aid in the clinical trials for amyloid plaque modifying therapeutics and once such drugs get approved this test could be an important screening test to select people that should be on such drugs.

Allen D. Roses, MD, FRCP (hon.), Duke University

Allen D. Roses has established an international reputation for his work in pharmacogenetics, exploratory drug discovery, and clinical neuroscience. Dr. Roses founded Cabernet Pharmaceuticals in 2008 to provide pharmacogenetics (PGx) and project-management services to pharmaceutical and biotechnology companies, clinical-research and managed-healthcare organizations, and academic institutions. He has formed a team of consultants with deep experience in the practical application of PGx to drug development. Dr. Roses also serves in several capacities at Duke University: as Jefferson-Pilot Professor of Neurobiology and Genetics, as Director of the Deane Drug Discovery Institute, and as Senior Scholar at the Fuqua School of Business. He recently returned to Duke after a decade-long career as a Senior Vice President at GlaxoSmithKline (GSK) and its corporate predecessor GlaxoWellcome (GW). Upon joining GW in 1997, he organized genetic strategies for susceptibility-gene discovery, pharmacogenetics strategy and implementation, and integration of genetics into medicine discovery and development. Subsequently at GSK, he headed research in clinical genetics, genomics, proteomics, pharmacogenetics, and bioinformatics in support of the entire R&D pipeline.

During his previous tenure at Duke, Dr. Roses was Jefferson Pilot Professor of Neurobiology and Neurology, Founding Director of the Joseph and Kathleen Bryan Alzheimer's Disease Research Center, Chief of the Division of Neurology, and Director of the Center for Human Genetics. He was one of the first clinical neurologists to apply molecular genetic strategies to neurological diseases. His laboratory reported the chromosomal location for more than 15 diseases, including several muscular dystrophies and Lou Gehrig's disease. He led the team that in 1992 identified APOE as a major, widely confirmed susceptibility gene in common late-onset Alzheimer's disease. Translation of these findings to metabolic-pathway analyses and drug discovery and development continued in GSK.

Dr. Roses was a member of the Science Board of the US Food and Drug Administration between 2003-2007. He was a member of the Board's Subcommittee on Science and Technology that in 2007 authored the report "FDA Science and Mission at Risk." He continues to consult with the FDA and other regulatory agencies in the field of pharmacogenetics and companion diagnostics.

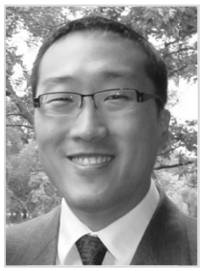
TOMM40 Genetic Biomarker: Accelerating Drug Development for Alzheimer's Disease and Frontotemporal Dementia

Allen D. Roses

Duke University, Durham, NC

TOMM40 is the name for the gene adjacent to APOE on chromosome 19 in LD, contains many polymorphic markers within its sequence [including introns]. A highly polymorphic polyT repeat variant [rs10524523] that is linked on the same strand to an APOE genotype variant. Our published work has described the relationship to the age of onset of symptoms leading to AD between the TOMM40-523 variant on each DNA stand and the APOE variant. We have constructed an algorithm based on TOMM40-523 genotypes, APOE genotypes and age that will be tested in combination as a "prognostic biomarker" for the design of a delay of onset of symptoms clinical trial in geographically collected populations of normal subjects, as defined by neuropsychological testing. In Alliance with Takeda Pharmaceuticals, we plan to evaluate the effect of pioglitazone in delaying the onset of cognitive impairment of the Alzheimer's type. TOMM40-523 is not a diagnostic test, or biomarker, for the diagnosis of AD until prospective PPV and NPV can be assessed. This will be done concurrently with the delay of onset trial. The pharmacogenetic enrichment of a high-risk population will use the 523 and APOE, with age of incident onset, as a prognostic pharmacogenetic biomarker. We have some additional data that may also support the involvement of TOMM40 in Frontotemporal Dementia as well.

William Hu, MD, PhD, Emory University School of Medicine



Dr. Hu is an assistant professor of neurology at the Emory University School of Medicine. He obtained his medical and graduate training at the Mayo Clinic, and post-doctoral training at the University of Pennsylvania.

His current research interests focus on developing and refining multi-modal biomarkers for neurodegenerative disorders including Alzheimer's disease, frontotemporal lobar degenerations, and amyotrophic lateral sclerosis.

CSF Biomarkers of FTLD-TDP and FTLD-Tau: A Multi-Center Study

William Hu

Emory University School of Medicine, Decatur, GA

It is challenging clinically to distinguish between different pathologic subtypes of frontotemporal lobar degeneration (FTLD). Recently, using cases with known pathology, we identified through targeted proteomics a panel of analytes that could distinguish between FTLD with TDP-43 pathology (FTLD-TDP) and FTLD with tau pathology (FTLD-tau). These analytes include Fas, neuropeptides (agouti-related peptide and adrenocorticotropic hormone), and chemokines (IL-23, IL-17). Classification by random forest analysis achieved high sensitivity for FTLD-TDP (86%) with modest specificity (78%). To validate these findings, we are recruiting 115 subjects from three academic centers with expertise in FTLD to undergo research CSF collection. Using a larger cohort of FTLD patients with known pathology, we will determine the sensitivity and specificity of this novel panel to distinguish between FTLD-TDP and FTLD-Tau. This presentation will give an update on the multi-center validation study for CSF FTLD biomarkers.

Judith Siuciak, PhD, The Biomarkers Consortium, Foundation for the National Institutes of Health

Dr. Judy Siuciak, Scientific Program Manager at The Biomarkers Consortium, manages the activities and projects of the Neuroscience Steering Committee. Prior to joining The Biomarkers Consortium, Dr. Siuciak spent 17 years working in industry where she directed in vivo pharmacology laboratories engaged in CNS drug discovery research. While at Pfizer and Bristol-Myers Squibb, her laboratory focused on developing novel therapies for schizophrenia, cognitive dysfunction and depression. Dr. Siuciak's early career was spent at Regeneron Pharmaceuticals, in Tarrytown, NY, where her laboratory focused on the neurochemical and behavioral effects of neurotrophic factors, and their role in depression and neurodegenerative diseases. Dr. Siuciak received her PhD in Neuropharmacology from the University of Illinois, College of Medicine. She is a co-inventor on two patents and has authored over 40 scientific publications in the field of Neuroscience and CNS drug discovery.

Use of Targeted Multiplex Proteomic Strategies to Identify Plasma and Cerebral Spinal Fluid-Based Biomarkers in Alzheimer's Disease

Judith Siuciak

Foundation for the National Institutes of Health, Inc., Bethesda, MD

The Foundation for the National Institutes of Health (FNIH) is the sole entity authorized by the U.S. Congress to raise private funds in support of NIH's mission of improving health through scientific discovery and translational research. Since 1996, FNIH has raised over $500 million towards over 100 projects, including the Alzheimer's Disease Neuroimaging Initiative (ADNI) and The Biomarkers Consortium (BC). The mission of the BC is to strengthen the evidence for using new and existing biomarkers to improve diagnosis, measure disease progression, guide treatment, accelerate drug development and target therapies to individuals in several therapeutic areas, including neuroscience. The BC includes broad participation from government, industry, academia and patient advocacy as well as other non-profit/private sector organizations.

The presentation will focus on two Biomarker Consortium projects which utilize Plasma and CSF samples from ADNI, respectively. These studies will compare samples from healthy controls to patients with Alzheimer's Disease or Mild Cognitive Impairment. In addition, comparisons will be made in MCI subjects who have progressed to dementia during the follow up period versus patients that had not progressed at the time of analysis.

José A. Luchsinger, MD, MPH, Columbia University

José Alejandro Luchsinger is a general internist and epidemiologist. Dr. Luchsinger has been working in risk factors for cognitive disorders including dementia and Alzheimer's disease since 1999. His focus has been predominantly in the relationships of vascular and metabolic risk factors and diet with Alzheimer's disease. He has been a co-investigator in a large cohort study of aging in New York City, and a principal investigator of a cohort study of cognition in persons with diabetes. He is also the principal investigator of a clinical trial of metformin, a medication for prevention of diabetes, in mild cognitive impairment. He leads the neurocognitive reading center of the Diabetes Prevention Program Outcomes Study, and cognition ancillary study to the Finnish Diabetes Prevention Program. He is the co-editor of the book "diabetes and the brain", and has published several important peer reviewed articles on the relation of diet, diabetes, adiposity, insulin resistance, and vascular risk factors in general with cognitive disorders.

Pilot Trial of Metformin in the Prevention of Alzheimer's Disease

José A. Luchsinger

Columbia University, New York, NY

Type 2 diabetes and its related condition, hyperinsulinemia, are related to a higher risk of Alzheimer's disease in observational studies. Laboratory and experimental studies support a role of type 2 diabetes and hyperinsulinemia in brain deposition of amyloid, the putative culprit of Alzheimer's disease. In addition, Type 2 diabetes and hyperinsulinemia are known to cause cerebrovascular disease, another important mechanism in Alzheimer's disease. These facts have prompted the hypothesis that preventing type 2 diabetes or decreasing hyperinsulinemia could prevent Alzheimer's disease. Metformin is a medication used for the treatment of Type 2 diabetes that is also effective and safe in its prevention. We hypothesized that metformin can decrease progression to dementia among overweight and obese persons without type 2 diabetes with amnestic mild cognitive impairment. We have been conducting a phase 2 clinical trial of metformin in persons with amnestic mild cognitive impairment that includes clinical, imaging and biomarker outcomes. Recruitment of the 80 participants of the trial is complete. The trial itself will finish in February of 2012 and we expect to report results in the Spring of 2012.

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