

The Alzheimer's Drug Discovery Foundation presents:

14th
**INTERNATIONAL
CONFERENCE ON
ALZHEIMER'S
DRUG DISCOVERY**

September 9-10, 2013

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 *14th International Conference on Alzheimer's Drug Discovery*.

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

We are deeply grateful to our generous sponsors whose support makes this meeting possible: Eli Lilly & Company, Merck Research Laboratories, Pfizer Inc., BioFocus, reMYND, and PsychoGenics. We would also like to thank our exhibitors: Amylgen, Zenobia, and Renovo Neural 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.

Engaging the next generation of research scientists in this field is more important than ever and we are pleased to announce our 2013 Young Investigator Scholarship winners. We encourage you to visit their poster presentations which will be displayed throughout the meetings.

To help us plan an even better conference in 2014, please complete the survey to provide us with feedback and suggestions.

Welcome, once again, to the *14th International Conference on Alzheimer's Drug Discovery*!

Best Regards,

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

ABOUT THE **ALZHEIMER'S** DRUG DISCOVERY FOUNDATION



Alzheimer's
Drug Discovery
Foundation

CONQUERING ALZHEIMER'S THROUGH DRUG DISCOVERY

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

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

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

WHAT WE'VE ACCOMPLISHED

- The ADDF has granted more than **\$62 million to fund 415 Alzheimer's drug discovery programs and clinical trials** in academic centers and biotechnology companies in **18 countries**.
- Many of the ADDF's grants are structured as loans or investments which provide a return that can be reinvested in new grants. From \$12.7 million invested to date in biotechnology company grants, **\$2.4 million has come back to the ADDF so far as returns on investment** – and has been committed to new 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 on a relevant topic in the field of neurodegeneration.

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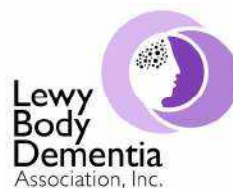
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2013 ADDF YOUNG INVESTIGATOR SCHOLARSHIPS

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 2013 Young Investigator Scholars are:

Yousuf O. Ali, PhD - Baylor College of Medicine

Sarah L. DeVos, PhD (cand.) - Washington University in St Louis

Jole Fiorito, PhD - Columbia University

Jing Guo, PhD - University of Pennsylvania, School of Medicine

Anselm H C. Horn, PhD - Friedrich-Alexander-Universität Erlangen-Nürnberg

Leen H. Kawas, PhD - M3 Biotechnology/Washington State University

Josien Levenga, PhD - New York University, School of Medicine

Steven H. Liang, PhD - Harvard Medical School and Massachusetts General Hospital

Antonett P. Madriaga, PhD (cand.) - University of Illinois at Chicago

Maninder Malik, MS - University of North Texas Health Science Center, Fort Worth, Texas

Hisham H. Qosa, PhD (cand.) - University of Louisiana at Monroe

Maria A. Telpoukhovskaia, PhD (cand.) - University of British Columbia

Liang Zhang, PhD - Mayo Clinic

PROGRAM

Monday, September 9	
8:00 – 8:30	Registration & continental breakfast
8:30 – 8:50	Welcome & Opening Remarks Howard Fillit, MD, Alzheimer's Drug Discovery Foundation
8:50 – 9:30	Plenary: From the Biology of Aging to the Prevention of Alzheimer's Disease Nir Barzilai, MD, Albert Einstein College of Medicine
SESSION I. Neuroprotection and Synaptic Plasticity	
Chair: Penny Dacks, PhD, Alzheimer's Drug Discovery Foundation	
9:30 – 9:35	Session Overview Penny Dacks, PhD, Alzheimer's Drug Discovery Foundation
9:35 – 9:55	Validation of a Novel Target Mechanism to Counter Progression of Alzheimer's Disease Lawrence Wennogle, PhD, Intra-Cellular Therapies Inc.
9:55 – 10:05	Q&A
10:05 – 10:25	Rescue of Neuronal Plasticity and Cognitive Impairment in Aged Rats <i>Funded through the ADDF-Charles River Partnership Program</i> Khalid Iqbal, PhD, New York State Institute for Basic Research in Developmental Disabilities
10:25 – 10:35	Q&A
10:35 – 11:05	BREAK
11:05 – 11:25	Development of Hepatocyte Growth Factor Mimetics for the Treatment of Neurodegenerative Disease Joseph Harding, PhD, M3 Biotechnology
11:25 – 11:35	Q&A
11:35 – 11:55	Preclinical Development of "Painless" Human Nerve Growth Factor Antonino Cattaneo, PhD, Scuola Normale Superiore and European Brain Research Institute
11:55 – 12:05	Q&A
12:05 – 12:25	The Dual LSD1/MAOB Inhibitor ORY-2001 Rescues the Memory Deficit in the Mouse SAMP8 Model for Accelerated Senescence Tamara Maes, PhD, Oryzon Genomics
12:25 – 12:35	Q&A
12:35 – 1:30	LUNCH AND POSTER SESSION
SESSION II. Mitochondrial Function and Energy Utilization	
Chair: Diana Shineman, PhD, Alzheimer's Drug Discovery Foundation	
1:30 – 1:35	Session Overview Diana Shineman PhD, Alzheimer's Drug Discovery Foundation
1:35 – 1:55	Lead Discovery of Novel Small Molecule Compounds Effective in Restoration of Mitochondrial Function Eugenia Trushina, PhD, Mayo Clinic
1:55 – 2:05	Q&A
2:05 – 2:25	ETB Receptor Agonist, IRL-1620, for the Treatment of Alzheimer's Disease Seema Briyal, PhD, Midwestern University
2:25 – 2:35	Q&A
2:35 – 2:55	Small Molecule P2X7 Antagonists for Alzheimer's Disease Treatment Paolo Pevarello, PhD, Axxam SpA
2:55 – 3:05	Q&A
3:05 – 3:25	Discovery of SIR Receptor-Selective Therapeutics Designed to Prevent or Slow the Progression of Alzheimer's Disease John Schetz, PhD, University of North Texas Health Science Center at Fort Worth
3:25 – 3:35	Q&A
3:35 – 3:45	BREAK
3:45 – 4:05	Characterizing the Mitophenotypes of Alzheimer's Disease: Peripheral Cell Biomarkers for Patient Selection and Measurement of Drug Response Marcie Glicksman, PhD, Harvard Neurodiscovery Center
4:05 – 4:15	Q&A
4:15 – 4:35	Pilot Trial of Metformin in the Prevention of Alzheimer's Disease Jose Luchsinger, MD, MPH, Columbia University Medical Center
4:35 – 4:45	Q&A
4:45 – 5:05	Evaluation of an mTOT Modulator Insulin Sensitizer as a Treatment for Alzheimer's Disease Jerry Colca, PhD, Metabolic Solutions Development Company
5:05 – 5:15	Q&A
5:15 – 5:20	Closing Remarks and Announcement of Young Investigator Awards Diana Shineman, PhD, Alzheimer's Drug Discovery Foundation
5:20 – 7:00	NETWORKING RECEPTION AND POSTER SESSION

Tuesday, September 10

8:00 – 8:30	Continental Breakfast
8:30 – 9:10	Plenary: Challenges and Opportunities in Repurposing FDA-Approved Drugs for Neurodegenerative Diseases Jeffrey Cummings, MD, ScD, Cleveland Clinic
SESSION III. Translatable Biomarkers to Accelerate Clinical Development 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	Glutamatergic Dysfunction in Cognitive Aging Disorders and a Therapeutic Target Ana Pereira, MD, The Rockefeller University
9:35 – 9:45	Q&A
9:45 – 10:05	Sartans to Slow Alzheimer's Disease Sandra Black, MD, FRCP(C), Sunnybrook Research Institute, University of Toronto
10:05 – 10:15	Q&A
10:15 – 10:35	Effect of Novel GLPI Analogue, Liraglutide on Microglial Activation and Cerebral Glucose Metabolism in Mild Alzheimer's Disease Paul Edison, MBBS, MRCP, MPhil, PhD, CCT, FRCPI, Imperial College London
10:35 – 10:45	Q&A
10:45 – 11:10	BREAK
11:10 – 11:30	A Phase IIa, Double Blind, Placebo-Controlled, Biomarker Study of Atomoxetine in Subjects with Mild Cognitive Impairment Allan Levey, MD, PhD, Emory University School of Medicine
11:30 – 11:40	Q&A
11:40 – 12:00	Blood Based Biomarkers of Neuronal and Microvascular Injury <i>Funded Through the ADDF-Lewy Body Dementia Association (LBDA) Partnership Program</i> Michelle Mielke, PhD, Mayo Clinic
12:00 – 12:10	Q&A
12:10 – 12:30	Development of Synaptic Biomarkers Related to AMPA-Receptor Trafficking in Alzheimer's Disease <i>Funded Through the ADDF-New York Academy of Sciences (NYAS) Challenge Grant</i> Douglas Galasko, MD, University of California, San Diego
12:30 – 12:40	Q&A
12:40 – 1:25	LUNCH AND POSTER SESSION
SESSION IV. ApoE, Tau and Protein Clearance Chair: Rachel Lane, PhD, Alzheimer's Drug Discovery Foundation	
1:25 – 1:30	Session Overview Rachel Lane PhD, Alzheimer's Drug Discovery Foundation
1:30 – 1:50	Modulation of Human apoE Isoform Levels as a Therapeutic Target Mary Jo LaDu, PhD, University of Illinois at Chicago
1:50 – 2:00	Q&A
2:00 – 2:20	Gene Delivery of Apolipoprotein E2 as a Treatment for Alzheimer's Disease Steve Paul, MD, Weill Medical College of Cornell University
2:20 – 2:30	Q&A
2:30 – 2:50	Translating Genetics into Biomarkers and Therapies: ApoE/Ab and ApoJ/Ab Complex Levels and Lipidation State as AD Biomarkers Modulated by VPA Steven Estus, PhD, University of Kentucky Research Foundation
2:50 – 3:00	Q&A
3:00 – 3:20	BREAK
3:20 – 3:40	Development of Screening Assays for Tauopathy in Stem Cell Derived Neurons Tae-Wan Kim, PhD, Columbia University Medical Center
3:40 – 3:50	Q&A
3:50 – 4:10	Proteasome Activators as Drug Candidates for Alzheimer's Disease Li Huang, PhD, Duke University
4:10 – 4:20	Q&A
4:20 – 4:40	Development of Small Molecule Enhancers of Autophagy for the Clearance of Protein Aggregates and Treatment of FTD <i>Funded through the ADDF-Association for Frontotemporal Degeneration (AFTD) Partnership Program</i> Wai Haung (Ho) Yu, PhD, Columbia University Medical Center
4:40 – 4:50	Q&A
4:50 – 5:00	Closing Remarks Howard Fillit, MD, Alzheimer's Drug Discovery Foundation

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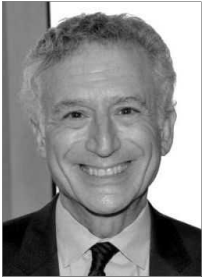


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BIOS AND ABSTRACTS

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

Nir Barzilai, MD, Albert Einstein College of Medicine



Dr. Barzilai is a Professor of Medicine and Genetics and the Director of the Institute for Aging Research at the Albert Einstein College of Medicine the home of two Centers of Excellence for the Biology of Aging. His interests focus on several basic mechanisms in the biology of aging, including the biological effects of nutrients on extending life. His studies on families with centenarians have provided genetic/biological insights on the protection against aging. Several drugs are developed based, in part, on these paradigm-changing studies.

Dr. Barzilai was awarded over \$25MM NIH funding for these efforts, has published over 200 peer-reviewed papers, and is a recipient of numerous prestigious awards. Dr. Barzilai has been a guest on The Today Show, CNN, ABC News and his research has been featured in many other publications and books.

From the Biology of Aging to the Prevention of Alzheimer's Disease

Nir Barzilai

Institute for Aging Research at Albert Einstein College of Medicine, Bronx, NY, USA

Aging is the major risk not only for AD but also for other diseases such as cancer, type 2 Diabetes mellitus and cardiovascular disease. We hypothesize that a progress in preventing these diseases will occur only if we can understand the reason people age at different rates, and develop strategy to delay aging.

Here we present examples derived from the aging field that have a direct relevance to drug development for AD:

Dwarfism in animals is associated with exceptional longevity compared with wild types (ponies, little dogs etc., and live longer). The problem is that low GH, and its main growth effector- IGF-I, are associated with more cognitive decline. We will show how shifting IGF-I activity from the periphery to the brain may prevent cancer and cognitive decline. Inhibitors to assure such effects have been developed.

We assume that centenarian's aging has been delayed and have implicated a longevity gene, cholesterol ester transfer protein (CETP), in the preservation of cognitive function in centenarians and their families. CETP inhibitor is in phase III trial to prevent CVD but offers an approach for prevention of AD.

We have discovered line of, previously un-noted mitochondrial derived peptides, whose expression declines with aging. Those peptides have roles in metabolism and stress response. One of those peptides, humanin, has been directly implicated in neuronal toxicity relevant to AD. Derivation of this molecule is tested for potential drug development for AD.

These examples suggest an approach of delaying aging and several of its disease, rather than focus on one organ-specific drug at a time.

I. Neuroprotection and Synaptic Plasticity

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

Validation of a Novel Target Mechanism to Counter Progression of Alzheimer's Disease

Lawrence Wennogle, PhD, Intra-Cellular Therapies, Inc.

Rescue of Neuronal Plasticity and Cognitive Impairment in Aged Rats

Khalid Iqbal, PhD, New York State Institute for Basic Research in Developmental Disabilities

Development of Hepatocyte Growth Factor Mimetics for the Treatment of Neurodegenerative Disease

Joseph Harding, PhD, M3 Biotechnology

Preclinical Development of "Painless" Human Nerve Growth Factor

Antonino Cattaneo, PhD, Scuola Normale Superiore and European Brain Research Institute

The Dual LSD1/MAOB Inhibitor ORY-2001 Rescues the Memory Deficit in the Mouse SAMP8 Model for Accelerated Senescence

Tamara Maes, PhD, Oryzon Genomics

SESSION CHAIR

Penny Dacks, PhD, Alzheimer's Drug Discovery Foundation



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

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

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

Lawrence Wennogle, PhD, Intra-Cellular Therapies, Inc.



Larry Wennogle received his PhD in Biochemistry from the University of Colorado, Boulder working under Dr. Howard Berg and in collaboration with Marvin Caruthers where he studied the structure of red blood cell membranes. He completed two post-doctoral positions, one at the University of Colorado and the second at the Pasteur Institute in Paris, France, working under Jean-Pierre Changeux on the structure-function of the nicotinic acetylcholine receptor from *Torpedo marmorata*. For the past 33 years, Dr. Wennogle has been involved in the research and development in the pharmaceutical industry aimed at discovery of novel pharmaceutical entities for human diseases. He was a Staff Scientist and Principal Research Fellow at Ciba-Geigy and

Novartis for 19 years, where he led drug discovery programs for Central Nervous System disorders, cardiovascular disease, diabetes and inflammation. Included in his experiences while at Novartis, he served on an “Expert Committee in Molecular Biology” with world-wide responsibility to evaluate new technologies.

With his broad expertise in drug discovery and the biochemical basis of disease, Dr. Wennogle supervises Intra-Cellular Therapies (ITI) development of small molecule therapeutics for neurodegenerative and neuropsychiatric disorders. ITI currently has a clinical candidate ITI-007 for schizophrenia in phase II clinical trials and another, ITI-214, in Phase I clinical development for cognitive impairment associated with schizophrenia. Dr. Wennogle is a Fellow of the New York Academy of Sciences and has co-authored over 60 scientific publications and 18 patents. He is a member of the New York Academy of Sciences, the American Association for the Advancement of Science, the American Chemical Society, Schizophrenia International Research Society and the Society for Neurosciences. Dr. Wennogle has adjunct appointments at Columbia University in the Department of Pharmacology and at Rutgers University Department of Molecular Biology and Biochemistry. His current focus is the development of novel therapeutics for cognitive dysfunction.

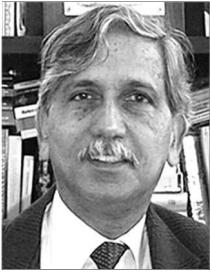
Validation of a Novel Target Mechanism to Counter Progression of Alzheimer’s Disease

Lawrence Wennogle

Intra-Cellular Therapies, Inc., New York, NY, USA

Intra-Cellular Therapies is developing novel therapeutic agents to treat disease progression of Alzheimer’s disease. One recent focus has been a kinase target involved in three aspects of the disease, namely amyloid beta production, tau hyperphosphorylation and disruption of normal circadian rhythms. This kinase, casein kinase I, is reported to be a major tau kinase. It is a “clock gene” known to regulate circadian gene expression. Inhibitors of CKI have been reported to reduce amyloid beta production in model systems. Novel therapeutic agents for Alzheimer’s disease are currently being developed based upon this target that represent distinct chemical classes devoid of off-target activity and displaying good oral bioavailability.

Khalid Iqbal, PhD, New York State Institute for Basic Research in Developmental Disabilities



Khalid Iqbal is Professor and Chairman, Department of Neurochemistry at the New York State Institute for Basic Research in Developmental Disabilities, Staten Island, New York. He received his PhD in Biochemistry in 1969 from the University of Edinburgh, Edinburgh, UK. Dr. Iqbal's pioneering studies on neuronal protein pathology and discoveries of tau protein and its abnormal hyperphosphorylation in Alzheimer's disease has won him many prestigious honors and awards, including the Potamkin Prize for Alzheimer Disease research from the American Academy of Neurology, and the Zenith Award from the Alzheimer's Association, USA. In 2007, Alzheimer's Association, USA, established a Khalid Iqbal Life Time Achievement Award for Alzheimer's Disease Research, which is given out annually at the International Conference on Alzheimer's Disease (ICAD) to a senior established Alzheimer disease researcher.

Dr. Iqbal has authored over 300 scientific papers in prestigious American and international scientific journals and edited seven books on research advances in Alzheimer's disease and related neurodegenerative disorders. He currently serves on the editorial boards of several journals and scientific advisory committees of biotechnology companies.

Rescue of Neuronal Plasticity and Cognitive Impairment in Aged Rats

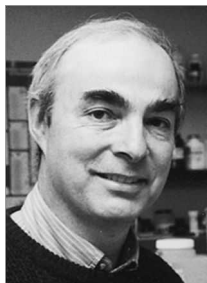
Khalid Iqbal

New York State Institute for Basic Research in Developmental Disabilities, Staten Island, NY, USA

Cerebral aging is in modern society not only a major public health problem but also is a great scientific challenge. At age 65 approximately 2.5% to 3% of individuals suffer from Alzheimer disease (AD) and this risk doubles every five years thereafter. AD is multifactorial and heterogeneous and involves several different etiopathogenic mechanisms. To date most of the efforts in developing therapeutics of AD have been to directly target A β or tau pathology. We have undertaken a different approach which involves shifting the balance from neurodegeneration to neural regeneration. Towards this end previously we developed a peptidergic neurotrophic compound called Peptide 021 and chronic treatment of a 3xTg-AD transgenic mouse model of familial AD with this compound was found to rescue deficits in neurogenesis and neuronal plasticity and cognitive impairment in these animals. To study the therapeutic potential of this further, we selected aged (19–21 month) Fischer rats which are known to show cognitive aging similar to that seen in sporadic AD. We had the aged rats chronically treated for three months by daily oral administration of Peptide 021 at the Charles River Labs, Kuopio, Finland. During the last two weeks of the treatment these animals were tested for spatial reference memory by Morris water maze and brain metabolism by IH-MRS and glucose metabolism by FDG-PET. We found that the aged animals were impaired in spatial reference memory as compared to normal young adult (2–3 month old) rats and this impairment was rescued in the Peptide 021-treated aged animals. Brain metabolism studies revealed, among others, a statistically significant increase in the level of myoinositol in the control aged animals which was rescued in the Peptide 021-treated animals. The aged rats also displayed a non-significant increase in the FDG consumption in various areas of the brain which was restored to the level seen in young adult animals. These results, obtained in an independent lab, provided a validation of the findings previously made in our lab in wild-type, Ts65Dn trisomic Down, and 3xTg-AD transgenic mice. The brains of the Peptide 021- and control vehicle-treated aged and young adult rats are currently being examined in our lab for the dentate gyrus neurogenesis and markers of neuronal plasticity. These findings demonstrate the therapeutic potential of Peptide 021 for the treatment of cognitive aging and AD.

Supported in part by the New York State Office of People with Developmental Disabilities and grant #20121203 from ADDF.

Joseph Harding, PhD, M3 Biotechnology



Dr. Harding received his PhD in Chemistry from the University of Delaware in 1974 and did postdoctoral training in the laboratory of Frank Margolis at the Roche Institute of Molecular Biology. He is a professor of physiology and neuroscience at Washington State University where he has been since 1976. His long term interest in peptides and peptidomimetics was initially focused on topics in olfaction and the central control of cardiovascular function. More recently his laboratory has turned their attention to the development of small molecule allosteric growth factor regulators as therapeutics for cancer and neurodegenerative. This work has spawned two biotechnology companies including M3 Biotechnology, which is developing small molecule hepatocyte growth factor antagonists for the treatment of various cancers and mimetics for the

treatment of neurodegenerative diseases.

Development of Hepatocyte Growth Factor Mimetics for the Treatment of Neurodegenerative Disease

Joseph Harding

M3 Biotechnology, Pullman, WA, USA

Enhancement of neurotrophic factor function has long been recognized as a potential treatment option for most neurodegenerative and neurotraumatic disorders. This should be no surprise given their role in the development, maintenance, and repair of the CNS and the need for augmented synaptogenesis, neurogenesis, and neuroprotection in the degenerating nervous system; processes that are the purview of these proteins. The difficulty, of course, is that these growth factor proteins are labile and blood-brain barrier (BBB) impermeable; characteristics that have necessitated the use of complex cell- and viral-based delivery systems that are invasive and costly. Our laboratory has exploited a common feature of many growth factor systems; namely the need to be activated by multimerization. We have exploited this activation step by constructing small allosteric activators (or antagonists) directed at the multimerization domains. Currently we have been focusing on hepatocyte growth factor (HGF) as a test case because of its role in cancer, fibrosis, regenerative activity, and cell survival and the overall potential of HGF-directed drugs as broad-based therapeutics. BBB permeable HGF mimetics, which display powerful synaptogenic activity and were demonstrated to reverse cognitive and motor deficits in several animal models, are currently being developed as treatment options for dementia and Parkinson's disease.

Antonino Cattaneo, PhD, Scuola Normale Superiore and European Brain Research Institute



Antonino Cattaneo is Professor of Neurobiology and Director of BioSNS Laboratory at the Scuola Normale Superiore (Pisa, Italy). He is also Scientific Coordinator at the European Brain Research Institute (EBRI Rita-Levi Montalcini Foundation) in Rome. His main current scientific interest is in the field of Alzheimer's disease, studying how an unbalance or defects in the signaling and processing of Nerve Growth Factor represent an upstream driver of neurodegeneration. Accordingly, he has been developing a variant of NGF (painless NGF) as a drug candidate for Alzheimer's disease, optimized to overcome the hurdles that limit the clinical applications of NGF.

Dr. Cattaneo has made significant original contributions to the field of antibody technologies, by developing the intrabody technology as a tool for achieving spatially and temporally localized protein interference in cells. He is currently exploiting this technology to study the cellular traffic and posttranslational processing of Abeta oligomers and tau in neurons. He has developed two humanized recombinant antibodies, respectively against NGF and NGF receptor TrkA, currently in clinical development by pharmaceutical industry for untreatable forms of chronic pain.

Preclinical Development of "Painless" Human Nerve Growth Factor

Antonino Cattaneo

BioSNS Laboratory, Scuola Normale Superiore, Pisa, Italy and European Brain research Institute, Roma, Italy

The clinical application of human Nerve Growth Factor (NGF) to prevent or slow human neurodegenerative diseases, and in particular Alzheimer's disease, has a strong scientific rationale, based on the actions of NGF on basal forebrain cholinergic neurons, but also on results linking alterations in the NGF/proNGF signaling to APP processing. Thus, deficits in the signalling processing of NGF have been proposed as an upstream driver for Alzheimer's neurodegeneration and the broad neuroprotective actions of NGF may hold a considerable therapeutic potential.

However, NGF delivery to the brain in a safe and long-term manner, limiting the adverse effects of NGF in activating nociceptive responses, has represented a significant challenge. Inspired by the Hereditary Sensory Autonomic Neuropathy type V (HSAN V) R100 mutation in the NGFB gene, we developed a human NGF double mutant (hNGFP61S/R100E, painless NGF), that displays identical neurotrophic properties to human NGF and has a greatly reduced ability to activate nociception. Moreover, hNGFP61S/R100E is traceable against endogenous NGF, via the tagging single point P61S mutation. We recently demonstrated that the non-invasive intranasal delivery of painless NGF in anti-NGF AD11 and in APPxPS1 mice leads to an effective rescue of memory impairments and AD-like neurodegeneration in these mice (Capsoni et al., *PLoS One* 2012).

We now report the results of a study aimed at assessing the therapeutic efficacy of hNGFP61S/R100E in transgenic mice harboring five familiar AD-related mutations (5xFAD mice), as well as at investigating, in the same group of animals, the absence or presence of nociception, after intranasal delivery. The recombinant hNGFP61S/R100E protein was produced in *E. coli* and purified after oxidative refolding, with a yield of around 10 mg per culture liter. We demonstrate that painless NGF, delivered for 1 month, starting from 3 months of age, i.e. after the onset of neurodegeneration, induces a complete rescue of spatial memory deficit and a decrease in the plaque load in 5XFAD mice. The mechanisms underlying these effects are linked to a clear rescue of synaptic dysfunctions, measured electrophysiologically in the entorhinal cortex, as well as to a reduction of microglia phagocytic activity and of pathological APP processing. The cellular and molecular targets of these actions are currently under investigation and the ongoing results will be reported. Moreover, we demonstrate that both acute and chronic intranasal administration of painless NGF does not trigger pain in 5XFAD mice, measured at the behavioural level, at the pharmacologically effective doses.

In conclusion, these findings confirm that painless NGF is a viable option to increase NGF activity in the brain in a non-invasive way, increasing its pharmacological therapeutic window and provide further proof that the neuroprotective activity of NGF goes well beyond the expected neurotrophic activity on cholinergic neurons.

Tamara Maes, PhD, Oryzon Genomics



Tamara Maes, PhD, is co-Founder, Vice President and Chief Scientific Officer of Oryzon genomics. The mission of the company is the identification of new biomarkers and their exploitation in diagnostics assays or as drug targets. Under Dr. Maes' leadership, the company completed the cycle of marker discovery to the commercial implementation of tests for the diagnosis of cancer, and developed small molecule drugs directed against the epigenetic target KDM1A/LSD1 for treatment of neurodegenerative disease and cancer. Dr. Maes holds a BA in Chemistry and a PhD in Biotechnology from the University of Ghent, Belgium.

The Dual LSD1/MAOB Inhibitor ORY-2001 Rescues the Memory Deficit in the Mouse SAMP8 Model for Accelerated Senescence

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

Oryzon Genomics, Barcelona, Spain

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disorder that culminates in severe dementia and death. Its etiology and pathogenesis are complex, encompass both genetic and environmental risk factors, and multiple pathogenic pathways are implicated in the disease.

Ubiquitin C-terminal hydrolase 1 (UCHL1), an enzyme involved in the recycling of polyubiquitin chains from proteins marked for degradation, is down-regulated in many neurodegenerative disorders, including Alzheimer's, Parkinson and Dementia with Lewy bodies. Individual carrying a mutant allele of UCHL1 develop a Parkinson like symptoms, and animal models confirm the relevance of this gene in neurodegenerative disease. The promoter region of UCHL1 contains binding sites for REST/NRSF (neuron restrictive silencer factor), a transcription factor that acts through a multi-protein complex including HDAC1/2, RCOR1/2, LSD1 and other components to repress REST target genes.

We are exploring the potential of LSD1 inhibitors to revert transcriptional changes observed in neurodegenerative disease and have developed potent specific LSD1 inhibitors and dual LSD1/MAOB inhibitors to test our hypotheses. Using a cell line with modest UCHL1 expression level (NB-4), we validated the hypothesis that inhibition of LSD1 can lead to transcriptional activation of UCHL1 expression. Treatment of SH-SY5Y cells with specific and dual LSD1 inhibitors revealed induction of many genes required for coordination of neuronal differentiation (ASCL1/MASH1), migration (FLNA), synapse integrity (CBLN2), memory and cognition (EHMT1) and neuronal survival (VIP).

We have developed ORY-2001, a dual inhibitor that inhibits LSD1 and MAO-B with equal potency (100nM) but that is selective over MAO-A (5uM). Preliminary ADME characterization shows ORY-2001 does not significantly inhibit CYP1A, CYP2C9, CYP2C19, CYP2D6, CYP3A, does not inhibit hERG and is not mutagenic in the AMES test. ORY-2001 can be orally administered and efficiently penetrates the blood brain barrier. A single dose of ORY-2001 protects mice from the deleterious effects of MPTP treatment on motor function and survival at doses between 0.3 to 30 mg/kg; illustrating that the compound efficiently inhibits MAO-B activity *in vivo*. ORY-2001 can be administrated safely in mice for extended periods and we used the compound to assess its efficacy on memory in the SAMP8 model.

SAMP8 mice present accelerated aging and many pathogenic alterations reminiscent of AD, including beta-amyloid deposition, increased expression of tau kinases, inflammation and oxidative stress. The brain-derived neurotrophic factor (BDNF), a key factor for learning and memory, is down-regulated in the brain of SAMP8 mice and several factors of the REST complex including RCOR1/2 and LSD1 were found to be up-regulated. ORY-2001 completely rescued the memory and learning defects of SAMP8 mice as determined by the performance of treated animals in the Novel Object Recognition Test (NORT). These results open the window for a new therapeutic approach and suggest LSD1 could be a novel target for Alzheimer disease.

II. Mitochondrial Function and Energy Utilization

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

Lead Discovery of Novel Small Molecule Compounds Effective in Restoration of Mitochondrial Function

Eugenia Trushina, PhD, Mayo Clinic

ET_B Receptor Agonist, IRL-1620, for the Treatment of Alzheimer's Disease

Seema Briyal, PhD, Midwestern University

Small Molecule P2X7 Antagonists for Alzheimer's Disease Treatment

Paolo Pevarello, PhD, Axxam SpA

Discovery of SIR Receptor-Selective Therapeutics Designed to Prevent or Slow the Progression of Alzheimer's Disease

John Schetz, PhD, University of North Texas Health Science Center at Fort Worth

Characterizing the Mitophenotypes of Alzheimer's Disease: Peripheral Cell Biomarkers for Patient Selection and Measurement of Drug Response

Marcie Glicksman, PhD, Harvard Neurodiscovery Center

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

José Luchsinger, MD, MPH, Columbia University Medical Center

Evaluation of an mTOT Modulator Insulin Sensitizer as a Treatment for Alzheimer's Disease

Jerry Colca, PhD, Metabolic Solutions Development Company

SESSION CHAIR

Diana Shineman, PhD, Alzheimer's Drug Discovery Foundation



Dr. Diana Shineman is the Director for 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 and development grants programs and strategic initiatives.

Dr. Shineman earned her PhD in Cell and Molecular Biology from the University of Pennsylvania (Penn). At Penn's 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 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, New York Academy of Sciences, and the Association for Women in Science, and has authored numerous peer-reviewed publications.

Eugenia Trushina, PhD, Mayo Clinic



Dr. Trushina is an Assistant Professor in the Department of Neurology and Department of Pharmacology and Experimental Therapeutics at the Mayo Clinic Rochester. She received her doctoral degree from Saratov State University in Russia. Dr. Trushina completed her postdoctoral training at the Mayo Clinic, Rochester where she worked with Drs. C. McMurray, R. Pagano and M. McNiven studying mechanisms of neurodegenerative diseases.

Dr. Trushina's laboratory is focused on the understanding the role of mitochondrial dysfunction in the etiology of 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 the NIH, BrightFocus, GHR and Mayo Clinic Research Awards.

Lead Discovery of Novel Small Molecule Compounds Effective in Restoration of Mitochondrial Function

Eugenia Trushina

Mayo Clinic, Rochester, MN, USA

Within our previous study funded by ADDF, we have demonstrated that tricyclic pyrone (TP) compound CP2 protected motor and memory decline in three transgenic mouse models of familial AD (FAD). We have found that (1) CP2 penetrates blood brain barrier and accumulates in brain tissue of CP2-fed animals; (2) long-term CP2 treatment (13 months) does not cause measurable side effects, does not affect animal development and breeding; (3) short (4 months) and long (13 months) - term CP2 administration via drinking water protected against memory decline and delayed the onset of motor phenotype in three mouse models of FAD; (4) CP2 treatment restored axonal trafficking of mitochondria in embryonic neurons from FAD mice; and (5) CP2 treatment restored brain energetics in FAD mice measured by metabolomics profiling. Original investigation into the mechanism of action using cellular models of AD suggested that CP2 prevents formation of amyloid beta oligomers and aggregates. However, our *in vivo* data suggest that the protection of memory and motor phenotype in FAD animals occurred with only modest reduction in amyloid burden. Thus, CP2 may possess amyloid-beta independent properties that ameliorate the AD phenotype. I will discuss our current progress toward the understanding of the molecular mechanisms behind CP2 action, and the approach we undertook together with the Nanosyn, Inc. to identify novel patentable molecules with CP2-like properties.

Seema Briyal, PhD, Midwestern University



Dr. Seema Briyal is currently an Adjunct Assistant Professor and Laboratory Manager at Midwestern University, Chicago College of Pharmacy. Dr. Briyal received her PhD in Pharmacology from All India Institute of Medical Sciences, New Delhi in 2006. Following postdoctoral research work at North Carolina State University, Dr. Briyal worked as Senior Research Associate in the Department of Pharmaceutical Sciences at Midwestern University - Chicago College of Pharmacy from 2009 to 2012.

Dr. Briyal has authored 19 peer-reviewed publications, and has more than 35 abstract presentations. Her work has appeared in a number of reputable journals including *Journal of Alzheimer's Disease*, *Brain Research*, *Life Sciences*, *Pharmacology Biochemistry and Behavior*, *Pharmacological Research and European Neuropsychopharmacology*.

Dr. Briyal is currently a member of *American College of Clinical Pharmacology* and serves as a member of the Editorial Board for *Indian Journal of Physiology and Pharmacology*. She is the winner of several awards including the C. L. Malhotra Award for best paper in Pharmacology and P. C. Dandiya Award for best poster presentation. She has guided the research of more than 15 graduate students and research fellows. Dr. Briyal's major research goals are to understand the molecular pathophysiology and develop novel therapeutic strategies for stroke and Alzheimer's disease. Currently, her studies focus on investigating molecular mechanisms of the endothelin system in neurological disorders, and testing the efficacy of endothelin-based therapeutic strategies for stroke and Alzheimer's disease.

ET_B Receptor Agonist, IRL-1620, for the Treatment of Alzheimer's Disease

Seema Briyal

Midwestern University, Downers Grove, IL, USA

Alzheimer's disease (AD) is a progressive brain disorder leading to impairment of learning and memory. Amyloid β ($A\beta$) induced oxidative stress has been implicated in the initiation and progression of AD. Endothelin (ET) and its receptors have been considered as therapeutic targets for AD. Recent studies indicate that stimulation of ET_B receptors may provide neuroprotection. A specific ET_B receptor agonist, IRL-1620, was found to reduce the infarct volume and promote neurovascular remodeling in rats with cerebral ischemia. The purpose of this study was to determine the effect of selectively stimulating ET_B receptors following $A\beta$ -induced cognitive impairment and oxidative stress in non-diabetic and diabetic (induced by streptozotocin) rats. Rats were treated with $A\beta_{1-40}$ (20 μ g in 3 equally divided doses; administered on day 1, 7 and 14) in the lateral cerebral ventricles using stereotaxically implanted cannula, experiments were performed on day 15. IRL-1620, a highly selective ET_B agonist, was administered alone or in conjunction with BQ788, an ET_B antagonist, chronically for 14 days. $A\beta$ treatment in non-diabetic and diabetic rats produced significant ($p < 0.0001$) increase in MDA levels (516.13 ± 14.02 and 531.58 ± 10.21 nmol/g wet tissue, respectively) compared to sham group (112.1 ± 1.82 and 114.31 ± 2.05 nmol/g wet tissue, respectively). Antioxidants (SOD and GSH) decreased following $A\beta$ treatment compared to sham group. Treatment with IRL-1620 reversed these effects, indicating that ET_B receptor stimulation reduces oxidative stress injury following $A\beta$ treatment. In Morris swim task, $A\beta$ treated rats showed a significant impairment in spatial memory. Rats treated with IRL-1620 significantly reduced the cognitive impairment induced by $A\beta$. BQ788 treatment completely blocked IRL-1620 induced reduction in oxidative stress and cognitive impairment. Results of the present study demonstrate that IRL-1620 prevents cognitive impairment and oxidative stress induced by $A\beta$, suggesting that ET_B receptor stimulation may be useful in neurodegenerative diseases.

Paolo Pevarello, PhD, Axxam SpA



Paolo Pevarello is a medicinal chemist with more than 30-year experience in different roles in the big and small pharmaceutical industry and in public research. He and his teams have been instrumental in the discovery of several clinical-stage compounds in the CNS and Oncology therapeutic areas.

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

Small Molecule P2X7 Antagonists for Alzheimer's Disease Treatment

Paolo Pevarello

Axxam SpA, Milan, Italy

The chronic neuroinflammatory process triggered by reactive microglia has emerged recently as an important factor in Alzheimer's Disease (AD). Several lines of evidence point towards the purinergic P2X7 ion channel as a central mediator of neuroinflammation. Therefore P2X7 antagonists with good CNS penetration may prove to be additional weapons for the treatment of neurodegenerative conditions.

Most P2X7 antagonists disclosed to date have been developed for peripheral (e.g. Rheumatoid Arthritis) rather than for CNS indications. As such they are not suitable as drugs targeting CNS diseases, such as AD.

We recently started a project aimed at finding P2X7 antagonists with good brain penetration to be validated in preclinical models of CNS diseases.

Through an HTS on our proprietary compound library we identified a novel chemotype for P2X7 antagonists with a good potential for development in a CNS setting.

The process leading to the identification of a suitable compound to be tested *in vivo* in AD animal models will be highlighted as well as the status reached by our most advanced compounds.

John Schetz, PhD, University of North Texas Health Science Center at Fort Worth



Dr. Schetz holds a BA in Chemistry from the University of Virginia and a PhD in Neuroscience from the University of Florida College of Medicine. He received post-doctoral training in radiolabeling, pharmacokinetics and metabolisms from the Department of Pharmacology at the University of Arizona College of Medicine, and molecular neuropharmacology training from the National Institutes of Health division of Molecular Neuropharmacology.

Currently, Dr. Schetz is a tenured Associate Professor in the Department of Pharmacology and Neuroscience at the University of North Texas Health Science Center in Fort Worth with cross-appointments in Psychiatry and Health Management and Policy. His continuing education includes certifications in molecular biology, and business incubator and management development programs. His professional activities include service on national and international grant review study sections, and his teaching responsibilities include course directorships in graduate and medical school curricula: Basic and Clinical Pharmacology, Nervous System I, Neurological and Psychiatric Disorders.

Dr. Schetz's research has been featured in print, radio and televised media reports. His lab team utilizes innovative and mechanistic approaches to advance knowledge and address societal needs of importance to medicine and the environment. A primary theme has been studies of molecular mechanisms and structure-activity relationships leading to practical applications in medicine and chemical biology. Selected research accomplishments include the first reporting of the allosteric mechanisms utilized by zinc ions to regulate G protein-coupled receptors (GPCR), achieving a molecular understanding of selective drug interactions with their receptor subtypes, discovering and developing subtype-selective compounds and PET imaging ligands, contributing to the mechanistic characterization of the atypical antipsychotic Abilify® (aripiprazole), and achieving a mechanistic understanding of the psychoactivity of a prominent HIV antiretroviral drug. His current research focuses on discovery and development of new therapeutic approaches for preventing or slowing the progress of Alzheimer's disease.

Discovery of SIR Receptor-Selective Therapeutics Designed to Prevent or Slow the Progression of Alzheimer's Disease

John Schetz

University of North Texas Health Science Center at Fort Worth, Fort Worth, TX, USA

Nitrosative stress is a critical mediator of the onset and progression of Alzheimer's disease (AD) as it both precedes and is associated with neuritic dystrophy and dendritic spine loss, A β /amyloid accumulation and deposition, cholinergic denervation and a memory loss phenotype in animal models of the disease. Under healthy conditions, nitric oxide (NO) is an important signaling molecule, and the enzyme that produces it, nitric oxide synthase (NOS), regulates ApoE and its other protein partners via nitrosylation. Under proinflammatory conditions (e.g. AD), oxidative stress upregulates NOS and the excess NO combines with oxygen radicals forming the reactive nitrosylating and nitrating species peroxynitrite which results in promiscuous dysregulation and indiscriminate damage. Because directly inhibiting NOS can produce systemic toxicity, our strategy is to selectively reduce NO activity at sites of inflammation by targeting Sigma-1 receptors (SIR) since they become important regulators of NOS activity only under conditions of oxidative stress. SIR receptors also appear to regulate neurotrophic factor responses. This has relevance to AD because Nerve Growth Factor (NGF)- and Brain-Derived Neurotrophic Factor (BDNF)-replacement therapies diminish cognitive impairment in animal models of AD and in neurotrophin trials in AD patients. Additional functional selection criteria for candidate compounds will thus include enhanced BDNF secretion or NGF-induced neurite sprouting. Our hypothesis is that elevated brain NO levels can be lowered at inflammatory sites by drugs that promote SIR-mediated reductions in NOS activity. If the same drugs simultaneously enhance neurotrophin responses, this is hypothesized to further reduce damage from an inflammatory insult. The path for discovery and proof-of-concept involves synthesis of novel candidate molecules with the appropriate receptor selectivity, drug-like characteristics and the desired in vitro and in vivo mechanistic profile. Novel high affinity SIR-selective candidates have been discovered and their drug-like properties are being refined for testing our target and mechanism-based hypothesis for therapeutics designed to slow the progression of AD.

Marcie Glicksman, PhD, Harvard Neurodiscovery Center



Marcie Glicksman, PhD, is the Co-Director of the Laboratory for Drug Discovery in Neurodegeneration (LDDN) which is focused on accelerating the identification of new therapeutics for central nervous system diseases. Dr. Glicksman has extensive experience in assay development, high throughput screening, as well as animal pharmacology and preclinical development. She has been in the field of drug discovery for more than 20 years, the most recent eight years at LDDN and thirteen years in the pharmaceutical industry. Previously, she was at Descartes Therapeutics focused on pain therapeutics and Cubist focused on anti-infectives. Prior to these positions, she was at DuPont-Merck and at Cephalon, Inc.

Dr. Glicksman has led multiple advanced programs for neurodegenerative diseases including co-inventorship of CEP1347, a drug candidate directed at a kinase that has been in Phase III clinical trials. She was elected (2005-2009) to the Board of Directors and served as Chairman of the Society for Biomolecular Sciences (now Society for Laboratory Automation and Screening). She is on the science advisory board for the Alzheimer's disease foundation (ADDF/ISOA) and the California Institute for Regenerative Medicine (CIRM), and reviews grants for NIH, the Michael J Fox, Alzheimer's Association, and Rett Foundations. She also regularly consults and this has included filing an Investigational New Drug application with the FDA, as well as projects involving the development of new technologies. Dr. Glicksman received a bachelor's degree from Brown University and a Ph.D. degree from Washington University.

Characterizing the Mitophenotypes of Alzheimer's Disease: Peripheral Cell Biomarkers for Patient Selection and Measurement of Drug Response

Marcie Glicksman

Harvard Neurodiscovery Center, Boston, MA, USA

Mitochondrial dysfunction in the brain is a feature of many, but likely not all, cases of AD. This is based on published data and supports the stimulation of mitochondrial activity as a therapeutic strategy. We hypothesize that if a patient population is selected based on their mitophenotype and response to drug in their peripheral cells, more effective clinical trials can be run. We have focused on robust and scalable phenotypic assays for mitochondria dysfunction in disease in order to demonstrate deficits in sub-populations of AD patients. In some cases response may be correlated with known genetic mutations, such as ApoE polymorphism and presenilin mutations. Our goal is to initiate a pilot study using peripheral blood samples on 50 patients and profile their mitophenotypes. And lastly, we will test the response of the patients' cells to drugs known to affect mitochondrial function. This approach can be applied to any cellular process that has been implicated in AD, for example, organelle transport, autophagy, or lysosomal function.

Jose Luchsinger, MD, MPH, Columbia University Medical Center



José Alejandro Luchsinger, MD, MPH, is an Associate Professor of Medicine and Epidemiology at Columbia University Medical Center in New York City. He is a general internist and epidemiologist who has conducted research in Alzheimer's disease risk factors, prevention, and consequences since 1999. Dr. Luchsinger has been the Principal Investigator or leader of several projects related to Alzheimer's disease including a project examining vascular risk factors in Alzheimer's disease in an elderly cohort, a cognition study of elderly diabetics, a cognition study in middle age participants, a study of Alzheimer's disease in Down's syndrome, a study of diabetes prevention, and a pilot clinical trial of metformin in the prevention of Alzheimer's disease. His research has been supported by several institutes of NIH, the Alzheimer's Association, the American Diabetes Association, the Fidelity Foundation, and the Alzheimer's Drug Discovery Foundation.

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

José Luchsinger

Columbia University Medical Center, New York, NY, USA

Diabetes and insulin resistance are related to a higher risk of Alzheimer's disease. Thus, strategies that prevent diabetes and reduce insulin resistance may be effective in preventing Alzheimer's disease. Following this hypothesis, we conducted a pilot randomized controlled trial of metformin, a medication effective in the treatment and prevention of diabetes, in the prevention of cognitive decline among 80 persons with amnesic MCI and without treated diabetes who were also overweight or obese. We found that after 12 months, persons in the metformin arm had better memory performance compared to those in the placebo arm as assessed with a test of recall while improving insulin resistance and inflammation. While biomarker outcomes did not show significant difference between the groups, they seemed to favor metformin. We believe that metformin should be tested in a larger clinical trial.

Jerry Colca, PhD, Metabolic Solutions Development Company



Jerry Colca, PhD, is a co-founder, part owner, and President/Chief Scientific Officer of Metabolic Solutions Development Company (MSDC; msdrx.com) in Kalamazoo, MI. He has spent his professional career studying the endocrine control of metabolism as relates to diabetes. Dr. Colca has a BS in Biology, a MS and PhD in Physiology and Biochemistry from the University of Houston where he studied the regulation of secretion of pancreatic hormones. His post-doctoral training at Washington University concentrated on the biochemistry of isolated pancreatic islets and the study of stimulus-secretion coupling in the control of metabolism.

Dr. Colca joined the Upjohn Company in 1984 to study to the mechanism of action of the thiazolidinediones and was instrumental in selection and development of pioglitazone hydrochloride (Actos®) as an anti-diabetic agent through Phase 2A clinical studies. The company formally known as Upjohn exited the insulin sensitizing field in 1993. Dr. Colca remained with the Upjohn Company through the mergers with Pharmacia, Monsanto-Searle, and Pfizer until he retired from the merged company in 2005. During this time he was leader of diabetes discovery team in Kalamazoo, helped build a new diabetes discovery effort in Sweden after the merger with Pharmacia, and finally building a new targets discovery effort in St. Louis after the Pfizer merger. Dr. Colca has been interested in the mechanism of action of the insulin sensitizer TZDs from the early days of their discovery and especially in the safety and pharmacology of pioglitazone. In January of 2006, he co-founded MSDC with Dr. Rolf Kletzien to take advantage of their unique insight into these molecules. The company has now grown to have two compounds in clinical trials and is making significant progress into understanding the molecular mechanisms of a new class of insulin sensitizers called mTOT modulators.

Evaluation of an mTOT Modulator Insulin Sensitizer as a Treatment for Alzheimer's Disease

Jerry Colca

Metabolic Solutions Development Company, LLC, Kalamazoo, MI, USA

Insulin sensitizers correct insulin resistance, a root defect in diabetes, and first generation of insulin sensitizers have been used primarily as a second line treatment for patients with diabetes since 1999. These compounds are limited by side effects secondary to activation of the nuclear receptor PPAR γ . MSDC is developing a new class of insulin sensitizers which work by modifying mitochondrial metabolism through a newly identified mitochondrial target (mTOT). The prototype mTOT modulator MSDC-0160 has demonstrated proof of concept in phase 2b diabetes trials. Since there is now considerable evidence that connects AD with diabetes and insulin resistance, here we have evaluated the effects of MSDC-0160 (qd, 150 mg) on non-diabetic patients with mild AD. The study was completed at a single site (Rush, Dr. Raj Shah) with evaluation of FDG-PET images by Abiant/ADMdx (Dawn Mathews). Three months treatment significantly increased circulating HMW adiponectin indicative of an improvement in insulin sensitivity as seen previously in the diabetic patients, although, as predicted, peripheral glucose levels, which were normal, did not change. Three months of treatment produced clear changes in the pattern of FDG-PET in the MSDC-0160-treated versus placebo group, which included the prevention of decline in posterior cingulate, parietal cortex angular gyrus, lateral temporal cortex, medial temporal cortex, and anterior cingulate-medial frontal cortex when referenced to the cerebellum as compared to the placebo group. This result suggests that MSDC-0160 is having central protective effects in these patients and forms the basis for the design of longer-term trials to evaluate whether mTOT insulin sensitizers can modify the underlying pathology in AD.

PLENARY SPEAKER

Jeffrey Cummings, MD, ScD, Cleveland Clinic



Jeffrey L. Cummings, MD, ScD, is Director, Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Nevada and Cleveland, Ohio. He is the Camille and Larry Ruvo Chair of the Neurological Institute of Cleveland Clinic and Professor of Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University. The Lou Ruvo Center for Brain Health is a clinical care, translational research, and clinical trials enterprise specializing in care of patients with neurocognitive deficits and development of new therapies for neurodegenerative disorders. Dr. Cummings' research and leadership contributions in the field of Alzheimer's disease have been recognized through the Henderson Award of the American Geriatrics Society (2006), the Research Award of the John Douglas French Alzheimer's Research Foundation (2008), and the Ronald and Nancy Reagan Research Award

of the national Alzheimer's Association (2008). In 2010, he received the Legacy Award from the Ticki Wilkerson-Kassel Movement Therapy Foundation and was honored by the American Association of Geriatric Psychiatry with their Distinguished Scientist Award. In 2011, he was awarded an honorary Doctor of Science by his Alma mater, University of Wyoming. Dr. Cummings is an experienced clinical trialist with expertise in clinical trial design and analysis, global trial implementation, and trial outcome measures. Dr. Cummings is the author of the Neuropsychiatric Inventory (NPI) which is the most commonly used tool for clinical trials characterizing behavioral disturbances in dementia syndromes. Dr. Cummings completed Neurology residency and a Fellowship in Behavioral Neurology at Boston University, Boston, Massachusetts. US training was followed by a Research Fellowship in Neuropathology and Neuropsychiatry at the National Hospital for Nervous Diseases, Queen Square, London, England. Dr. Cummings was formerly Professor of Neurology and Psychiatry at UCLA, director of the Mary S. Easton Center for Alzheimer's Disease Research at UCLA, and director of the Deane F. Johnson Center for Neurotherapeutics at UCLA. He is past president of the Behavioral Neurology Society and of the American Neuropsychiatric Association. Dr. Cummings has authored or edited over 35 books and published 600 peer-reviewed papers.

Repurposed Drugs in the Treatment of Alzheimer's Disease

Jeffrey Cummings

Cleveland Clinic, Las Vegas, NV, USA

Repurposing is the therapeutic use of a drug or drug candidate for a disease other than that for which it was originally intended. Repurposing can involve capitalizing on the known mechanism of action in the original condition for use in a new condition, building on a newly discovered mechanism of action of an approved compound, or reviving a compound abandoned for commercial reasons. Repurposed compounds have advantages because of the information already generated about them. Repurposed compounds have known druggability, pharmacokinetics, dose for the original indication, side effects, formulation, manufacturing, distribution and pricing. Unknown, are the efficacy in the new condition, the dose for the new condition, side effects associated with the population having the new condition, or drug-drug interactions relevant to the new condition. Repurposed agents often have challenges regarding intellectual property. Approaches to this have included developing patents regarding dose, formulation, method of use and geographic distribution. Repurposing studies may result in the use of the compound in a new indication, repurposing successes may establish interest in a specific pathway; or the compound may serve as a lead molecule for a series to be optimized for the new condition. In a review of approved drugs possibly available for repurposing because of preliminary evidence of efficacy in Alzheimer's disease, we identified thirteen anti-hypertensives, thirteen psychotropics, seven diabetes compounds, four oncology compounds, three immunotherapies, two anti-epileptic drugs and six miscellaneous drugs. We have initiated a new program to accelerate clinical trials in Alzheimer's disease utilizing repurposed compounds. This includes a novel scoring method, use of biomarker outcomes, implementation of novel cognitive measures, use of novel trial technology, implementation of an innovative database and planned combination therapy. The program represents an opportunity to recycle drugs sequentially. Repurposing provides exiting opportunities but also has limitations. Repurposing is conservative and will not identify new types of molecules. There are intellectual property concerns and possibly limited pharmaceutical company interest. Repurposing may encourage off-label prescribing and may cause "drop-ins" in trials. Development of repurposed agents demands a thorough understanding of the pros and cons of repurposing.

III. Translatable Biomarkers to Accelerate Clinical Development

Chair: Howard Fillit, MD, Alzheimer's Drug Discovery Foundation

Glutamatergic Dysfunction in Cognitive Aging Disorders and a Therapeutic Target

Ana Pereira, MD, The Rockefeller University

Sartans to Slow Alzheimer's Disease: Proof of Concept

Sandra Black, MD, FRCP(C), Sunnybrook Research Institute, University of Toronto

Evaluating the Effect of Novel GLPI Analogue, Liraglutide in Alzheimer's Disease (ELAD)

Paul Edison, MBBS, MRCP, MPhil, PhD, CCT, FRCPI, Imperial College London

Repurposing Atomoxetine as a Novel Anti-Inflammatory Strategy for Neuroprotection in Mild Cognitive Impairment

Allan Levey, MD, PhD, Emory University School of Medicine

Development of Sphingolipid Biomarkers for Alzheimer's Disease and Lewy Body Dementia

Michelle M. Mielke, PhD, Mayo Clinic

A Novel Synaptic Biomarker in Cerebrospinal Fluid in Alzheimer's Disease

Douglas Galasko, MD, University of California, San Diego

Ana Pereira, MD, The Rockefeller University



Dr. Ana C. Pereira graduated in Medicine at Universidade Federal de Sao Paulo, Brazil in the top 1% of the class. She was a Post-Doctoral Research Scientist at Columbia University at the Taub Institute for Alzheimer's Disease investigating adult neurogenesis with brain imaging techniques in animals and humans.

She completed Residency in Neurology at Harvard University and received subspecialty training in Cognitive Neurology at Columbia University. She is currently an Instructor in Clinical Investigation at the Rockefeller University.

Glutamatergic Dysfunction in Cognitive Aging Disorders and a Therapeutic Target

Ana Pereira

The Rockefeller University, New York, NY, USA

Cognitive decline, either age-related or due to Alzheimer's disease, is a major problem in an increasingly aging population. This leads to memory loss and decreased executive function that significantly affect daily living, often placing a great burden and cost to society to care for those individuals. There is an urgent unmet need to understand, prevent, and treat cognitive aging disorders.

It is notable that the same circuits that are vulnerable to degeneration in Alzheimer's disease are also vulnerable to synaptic alterations without neuron death that are characteristic of age-related cognitive decline. Those selectively vulnerable circuits are comprised of glutamatergic pyramidal cells that furnish corticocortical connections between the association cortices along with the hippocampal formation, required for cognition. It is unknown how the glutamatergic system makes the shift from age-related cognitive decline to degeneration as the same circuits are vulnerable. The central working hypothesis of Dr. Pereira's work is that dysregulated and hyperactive glutamatergic circuits contribute to neurodegeneration and significant cognitive decline. Glutamate binds to synaptic NMDA receptors to stimulate neuronal activity, but excessive glutamate activates extra-synaptic NMDA receptors driving excitotoxicity and neuronal death. The cause of the overactive glutamatergic circuitry is not yet fully understood, however animal models and human preliminary data suggest that hypoxia (such as in the condition of sleep-disordered breathing) cause increased glutamate levels. Dr. Pereira also investigates the use of glutamate modulators in animal models of aging to treat cognitive impairment, with analysis of behavioral and detailed structural brain changes that represent neural plasticity and is conducting a pilot clinical trial with a glutamate modulator in patients with mild Alzheimer's disease. Glutamatergic dysregulation is also intimately associated with beta amyloid and phosphorylated tau, the pathogenic proteins in Alzheimer's disease, in addition to glutamate-mediated excitotoxicity that leads to neuronal loss. She evaluates the impact of a potential better regulation of the glutamatergic synapse in the Alzheimer's trial with measures of cognitive functional changes along with brain imaging biomarkers such as magnetic resonance spectroscopy and FDG-PET.

Sandra Black, MD, FRCP(C), Sunnybrook Research Institute, University of Toronto



Sandra Black, MD, FRCP(C), is an internationally renowned cognitive and stroke neurologist who holds the inaugural Brill Chair in Neurology, Department of Medicine, University of Toronto and Sunnybrook Health Sciences Centre. She was appointed to the Order of Ontario in 2011 and elected as a Fellow of the Royal Society of Canada in 2012. A leading clinical trialist in dementia, she is the current Executive Director of the Toronto Dementia Research Alliance. She is a key founder of the Heart & Stroke Foundation Centre for Stroke Recovery, a multi-site, public-private, non-profit research corporation focused on maximizing stroke recovery, including covert stroke.

Currently, Dr. Black is the Brain Sciences Research Program Director at Sunnybrook Research Institute. She has received awards for outstanding mentorship of junior faculty, post-doctoral fellows and graduate students. Her 30-year research career has bridged dementia and stroke, exploiting advanced neuroimaging techniques for detection, differential diagnosis, monitoring outcomes and studying brain-behavior relationships, with a recent focus on interactions of aging, small vessel disease, Alzheimer's Disease, and stroke. She has authored/co-authored 340 peer-reviewed papers, 65 invited publications and serves on a number of international advisory groups on stroke and dementia. She combines enormous dedication to patients with cutting-edge science.

Sartans to Slow Alzheimer's Disease: Proof of Concept

Sandra Black

Sunnybrook Research Institute, University of Toronto, Toronto, Canada

Hypertension has emerged in epidemiological studies as an important risk factor not only for heart attacks and stroke, but also for Alzheimer's disease (AD) and overall brain health. Uncontrolled hypertension in midlife was independently associated with Alzheimer brain pathology 36 years later in the Honolulu Aging study. One randomized double-blind study (the Syst-Eur Study) convincingly showed that treatment of hypertension with a calcium channel blocker prevented decline to dementia over a four-year period. Comparative trials in hypertensive individuals between ACE inhibitors (ACEI) and angiotensin receptor blockers (sartans) have generally failed to show differences in emergent dementia, but sample sizes have often been insufficient to address this question adequately. A recent systematic review of randomized and observational studies showed that antihypertensive treatment regardless of drug class benefitted cognition and reduced risk of all-cause dementia, but that sartans provided the largest benefit. There is a strong rationale for a more detailed comparative study of outcomes in studies of ACEI vs. sartans: it has been recently established that ACEI increase toxic Amyloid Beta 40-42 peptides in the brain, whereas sartans in contrast, promotes their catabolism, and also have memory enhancing effects through long-term potentiation, shown in animal models. A recent large autopsy study suggested that the sartan users (15% of the 890 subjects in the sample) had lowered risk of clinical AD and less amyloid pathology.

Hence, we are undertaking a randomized, open-label, rater-blinded, head-to-head proof-of-concept study of a sartan (telmisartan) vs. an ACEI (perindopril) in 240 hypertensive mild-moderate AD patients. Our primary objective is to determine the comparative efficacy and safety of telmisartan vs. perindopril in reducing brain atrophy, as indexed by ventricular enlargement, over one year. Our secondary aims are to assess the responsiveness of cognitive, neurobehavioral and functional measures to treatment with telmisartan vs. perindopril and to obtain pilot data on the utility of multi-modal MRI (including DTI and resting state MRI) as possible surrogate biomarkers for treatment intervention. Patients will undergo full cognitive, behavioral and functional assessments at baseline, 6 months and 12 months, with briefer assessments and BP check every 3 months. Quantitative structural MRI will be obtained using a protocol similar to ADNI. Diffusion Tensor Imaging and resting state functional MRI will be obtained at baseline and one year. Additional caregiver burden and economic analyses will also be performed.

If the results are promising, this could power a more definitive study, which could have pragmatic, practice-changing implications, especially for hypertension control in AD subjects, since sartans are relatively less often used than ACEI's in common clinical practice. This could repurpose a well-known class of drugs widely used for hypertension and coronary artery disease. It would also be one of the first trials in AD to use ventricular enlargement as a primary surrogate outcome to test proof of concept and to determine whether further investigation is warranted.

Paul Edison, MBBS, MRCP, MPhil, PhD, CCT, FRCPI, Imperial College London



Dr. Edison is a Clinical Senior Lecturer in Centre of Neuroscience at Imperial College London and Consultant Physician at Hammersmith Hospital, London.

Dr. Edison's research has focused on neuroimaging using novel molecular probes and magnetic resonance techniques for imaging pathophysiological changes associated with Alzheimer's disease, Parkinson's disease, and other neurodegenerative diseases. He has extensive experience in PET imaging in different neurodegenerative and neuroinflammatory conditions. Combined with his clinical expertise in different types of degenerative diseases and dementia, he has investigated the relationship between amyloid deposition, microglial activation, and glucose metabolism in different disorders along with evaluating different transporters in brain. His work in assessing microglial activation and amyloid load showed that both these are increased in AD, and microglial activation correlates with cognition, while amyloid load does not correlate with cognition.

Currently, Dr. Edison's work focuses on neuroinflammation, and the interplay between inflammation and immunity in neurodegenerative and neuroinflammatory disease, and relating these with the genetic information. He is also evaluating the methods of modulating inflammation and amyloid in Alzheimer's disease. He is the chief investigator for several clinical studies.

Dr. Edison was an MRC clinical research fellow and currently is a HEFCE clinical senior lecturer. He is a Fellow of Royal College of Physicians of Ireland, Member of Royal College of Physicians UK, Member of American Academy of neurology and various other professional organizations.

Dr. Edison leads dementia service at Imperial College London and Imperial College Healthcare NHS trust.

Evaluating the Effect of Novel GLPI Analogue, Liraglutide in Alzheimer's Disease (ELAD)

Paul Edison

Imperial College London, London, UK

Insulin resistance has been identified as a risk factor for AD. The newer anti diabetic drug, GLP-I incretin analogue, Liraglutide is being used safely in diabetic patients. It was shown in extensive preclinical studies that liraglutide has a range of neuroprotective properties in mouse models of AD. Liraglutide crosses the blood-brain barrier, protects the cognitive abilities of mice, reduces amyloid plaque formation in the murine brain, reduces the associated inflammatory response, reduces levels of soluble amyloid oligomers, normalizes synaptic plasticity in the hippocampus, normalizes glucose uptake in the frontal brain and finally increases the proliferation of neuronal progenitor cells and the number of new neurons in the dentate gyrus. These findings are supported by other published information on the neuroprotective properties of GLP-I analogues. Liraglutide can be easily administered through daily subcutaneous injections and does not cause hypoglycaemia in non-diabetic individuals. In this study we aim to evaluate the effect of Liraglutide on cognition and other biomarkers (cerebral glucose metabolism, MRI volume, CSF biomarkers) in mild Alzheimer's disease. Other outcome measures will include microglial activation, functional status, behavioral and neuropsychiatric measures as well as biomarkers to explore the mechanism of action of this intervention on AD pathology.

Allan Levey, MD, PhD, Emory University School of Medicine



Allan Levey is Professor and Chairman of the Department of Neurology at Emory University, Director of the Emory Alzheimer's Disease Research Center and Founding Director of the Emory Center for Neurodegenerative Disease. He received a BS from University of Michigan and an MD/PhD (Immunology) from the University of Chicago; trained in neurology at Johns Hopkins, and molecular biology at the National Institutes of Health.

Dr. Levey is a neurologist and neuroscientist internationally recognized for his work in neurodegenerative disease. He has more than 250 research publications in neurodegenerative disorders including Alzheimer's and Parkinson's diseases. He was named an ISI Highly Cited Researcher in the field of *Neuroscience*.

Repurposing Atomoxetine as a Novel Anti-Inflammatory Strategy for Neuroprotection in Mild Cognitive Impairment

Allan Levey

Emory University School of Medicine, Atlanta, GA, USA

The locus coeruleus (LC) is the first site of identifiable pathology in Alzheimer's disease (AD), and among the most consistently and selectively groups of neurons affected in the disease. With widespread connections throughout nervous system, traditional views of LC function include its key roles in attention and memory, arousal and behavioral state control, and emotions and stress responses. Degeneration of LC is generally believed to contribute to cognitive and behavioral symptoms of AD. However, recent studies implicate LC as a critical regulator of innate immune function and suggest a more direct link to AD pathogenesis. Specifically, selective LC lesions in animal models of AD demonstrate that loss of LC-derived norepinephrine (NE) incites a neurotoxic pro-inflammatory condition, reduces A β clearance and negatively impacts cognition – recapitulating key aspects of AD. Remarkably, restoration of NE levels reverses these effects and slows neurodegeneration in AD animal models, raising the possibility that treatments that increase NE transmission may have the potential to delay AD-related pathology. These findings provide rationale for a pilot study of atomoxetine, an FDA-approved NE transport inhibitor for attentional disorders, with an excellent safety profile. Repurposing atomoxetine may provide an immediately available NE-enhancing therapy to retard neurodegeneration in AD, in addition to providing potential symptomatic benefits. Since mild cognitive impairment (MCI) coincides with the onset of clinical symptoms and LC pathology is already present at this early stage of AD pathogenesis, MCI may offer a critical window of time to initiate NE-based therapies aimed at the secondary wave of events that lead to progressive neurodegeneration. These considerations provide rationale for a phase II trial of atomoxetine in MCI, seeking supportive evidence for its novel anti-inflammatory mechanism of action and neuroprotective therapeutic potential.

Michelle Mielke, PhD, Mayo Clinic



Michelle M. Mielke, PhD, received a BS in Neuroscience at the University of Pittsburgh and a PhD in Psychiatric/NeuroEpidemiology from the Johns Hopkins University Bloomberg School of Public Health. She then completed a two-year fellowship as the Lydia Gillespie Clinical and Research Post-doctoral Fellow in Psychiatry. Dr. Mielke was on faculty at the Johns Hopkins University School of Medicine for four years, prior to joining the Mayo Clinic in 2011. She is currently an Associate Professor in the Department of Health Sciences Research, Division of Epidemiology, at the Mayo Clinic in Rochester, MN.

Dr. Mielke works as a translational epidemiologist to further understanding of the etiology and epidemiology of neurodegenerative diseases and neuropsychiatric disorders. A primary focus of her research is the identification of fluid and neuroimaging biomarkers for the diagnosis, prediction, and/or progression of Alzheimer's disease. Much of her work has emphasized the utility of blood-based lipids, especially the role of sphingolipids (ceramides and sphingomyelins) in the clinical development of AD and in relation to AD pathology. She is also examining the relationship between sphingolipids and alpha-synuclein-related dementias. Dr. Mielke is the PI of several NIH and Foundation-funded clinical and epidemiological-based grants examining blood-based biomarkers of Alzheimer's disease and other neurodegenerative conditions.

Development of Sphingolipid Biomarkers for Alzheimer's Disease and Lewy Body Dementia

Michelle M. Mielke

Mayo Clinic, Rochester, MN, USA

Sphingolipids may be important biomarkers and treatment targets for Alzheimer's Disease (AD) and Dementia with Lewy Bodies (DLB). Sphingomyelins are critical components of lipid rafts, which are important in cellular processes and second messenger systems, and also affect the processing of amyloid precursor protein. Ceramides are second messengers that regulate cellular differentiation, proliferation, and apoptosis, and promote free radical generation. Ceramides have been associated with amyloid-beta and tau levels in pre-clinical animal and cellular models. Our research translating these findings to examine these sphingolipids in relation to risk of AD and AD pathology will be discussed. Additionally, several studies have demonstrated the involvement of lipids in the development and progression of DLB. Mutations in GBA are associated with significantly higher odds of Lewy body pathology among Parkinson's disease patients. Glucocerebrosidase catalyzes the breakdown of the glycolipid glucosylceramide to ceramide and glucose. We have begun to plasma levels of ceramide and glucosylceramide as biomarkers for DLB. New results linking these lipids to alpha-synuclein pathology will be presented.

Funded Through the ADDF-Lewy Body Dementia Association (LBDA) Partnership Program

Douglas Galasko, MD, University of California, San Diego



Dr. Douglas Galasko is a Neurologist in the Department of Neurosciences, University of California, San Diego and Director of the Shiley-Marcos Alzheimer's Disease Research Center. His research interests include development of biomarkers for Alzheimer's Disease and other neurodegenerative disorders.

A Novel Synaptic Biomarker in Cerebrospinal Fluid in Alzheimer's Disease

Douglas Galasko, Paul Worley

University of California, San Diego, La Jolla, CA, USA

Synaptic damage is a prominent feature of Alzheimer's Disease (AD) pathology. In clinical-pathological studies, measures of synaptic markers (such as synaptophysin) correlate strongly with cognitive test measures obtained close to the time of death in AD. We have explored secreted proteins that play a role in maintaining synaptic strength, and are important in the regulation of long term potentiation (LTP), a mechanism important in memory and learning. We focused on Neuronal Pentraxins (NPTX's), which mediate aspects of activity-mediated neuroplasticity. For example, in its role as a regulator of homeostatic plasticity, NPTX2 is required to increase inhibitory circuit function in response to increased brain activity.

In postmortem brain tissue samples, NPTX2 was markedly decreased in patients with AD compared to controls and NPTX1 to a lesser extent. NPTX1 and NPTX2 were measurable in CSF on Western blot. Quantitation using Western analysis showed decreases in CSF levels of these molecules in MCI and AD, and their levels correlated with MMSE scores. Their levels did not correlate with those of A-beta42, but did show a correlation with tau and P-tau181. These synaptic proteins may provide markers related to the progression of AD.

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

IV. ApoE, Tau and Protein Clearance

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

Modulation of Human apoE Isoform Levels as a Therapeutic Target Using a New Alzheimer's Disease Transgenic Mouse Model

Mary Jo LaDu, PhD, University of Illinois at Chicago

Gene Delivery of Apolipoprotein E2 as a Treatment for Alzheimer's Disease

Steve Paul, MD, Weill Medical College of Cornell University

CSF Levels of apoE and apoJ Complexes with A β

Steven Estus, PhD, University of Kentucky Research Foundation

Development of Screening Assays for Tauopathy in Stem Cell Derived Neurons

Tae-Wan Kim, PhD, Columbia University Medical Center

Proteasome Activators as Drug Candidates for Alzheimer's Disease

Li Huang, PhD, Duke University

Enhancement of Autophagy and Clearance of Tau

Wai Haung Yu, PhD, Columbia University Medical Center

SESSION CHAIR

Rachel Lane, PhD, Alzheimer's Drug Discovery Foundation



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

Dr. Lane earned her PhD in Molecular Biology and Biotechnology from the University of Sheffield, United Kingdom before completing three years of postdoctoral training at the Mount Sinai School of Medicine in New York. Dr. Lane's postdoctoral research, in a team led by Dr. Sam Gandy, uncovered common mechanistic links between Alzheimer's disease and type 2 diabetes mellitus.

In addition to her experience in basic research, Dr. Lane gained experience in drug development through her position as an Analyst Intern at a New York based Venture Capital firm and the Fundamentals of the Bioscience Industry Program at New York's Stony Brook University, for which she received a Directors Scholarship. She is a member of the Society for Neuroscience and the New York Academy of Sciences and has published numerous first authored research publications and reviews in peer reviewed journals.

Mary Jo LaDu, PhD, University of Illinois at Chicago



Mary Jo LaDu, PhD, is Associate Professor of Anatomy and Cell Biology at the University of Illinois at Chicago. Dr. LaDu's research focuses on the structural and functional interactions between apoE and A β in the CNS.

Prior to this, Dr. LaDu was a Principal Investigator at the Northwestern Research Institute (1999-2005) and a Research Assistant Professor at the University of Chicago Medical Center (1997-1999).

Dr. LaDu obtained her PhD in Physiology from the University of Illinois at Chicago.

Modulation of Human apoE Isoform Levels as a Therapeutic Target Using a New Alzheimer's Disease Transgenic Mouse Model

Mary Jo LaDu

University of Illinois at Chicago, Chicago, IL, USA

APOE4 is the greatest genetic risk factor for sporadic Alzheimer disease (AD), increasing lifetime risk up to 60-fold compared to APOE3. Aggregates of A β plaques are a requisite hallmark of AD, and apoE levels are thought to modulate the levels and neurotoxicity of A β . However there is much debate on whether to raise or lower apoE levels as an AD therapeutic approach. Recent evidence by Cramer and co-workers demonstrated that bexarotene (BEX, an RXR agonist) increased apoE levels and decreased soluble A β within hours and significantly reduced insoluble A β after three days, although plaque levels at 3-months were unchanged. However, application of these data to AD patients is difficult as the studies used transgenic mice producing human A β (A β -Tg) but expressing mouse-apoE. However, experimental evidence suggests that increasing human-apoE4 will increase A β levels, thus actually increasing AD pathology. Despite this major contraindication, BEX is entering clinical trials for treating AD patients. Thus, it is imperative that the effects of BEX on the human forms of apoE are tested, specifically apoE4. Even if proven efficacious in the presence of human apoE, BEX may be less selective for RXR than other available RXR-agonists (for example, LG268) and thus may not be the optimal clinical candidate. The purpose of this proposal is to compare the effect of BEX with LG268 in new transgenic mice that express human apoE3 or apoE4 and over-express human A β 42 (EFAD Tg-mice). A recent series of studies published as Letters in Science addressed the reproducibility of the original observations by Cramer et al. In general, indirect target engagement was established by significant increases in ABCA1 expression. Tentative conclusions indicate that Bex has no effect on apoE levels, lowers soluble A β (defined as either ISF or TBS extracted) but has no effect on extracellular A β . This may lead to improved cognition. However, hepatic toxicity was a major concern, as was the PK/PD analysis, which varied with the source of drug and mode of delivery. The only study to use an A β -Tg model expressing human apoE3 and E4 reported no difference. For our studies, the first important question that we addressed was whether Bex and LG2576 reached the brain in mice, as they were developed as the anti-cancer drugs for peripheral organs. We demonstrated that both compounds crossed into the brain, and identified the optimal oral single daily dose to give the mice. Our next goal was to determine the effect of BEX and LG268 after short-term treatment in E3FAD and E4FAD mice. For short-term treatment, EFAD mice were aged to 5 months + 3 weeks, and treated for 7 days with the equivalent of a single daily dose of Bex, LG268 or control by oral gavage. To determine whether an oral single daily dose or a sustained low drug concentration over a week is the best treatment method, we also treated mice with a novel method of drug delivery called hydrogel, which the mice drink instead of water through their awake period to achieve a constant drug concentration through-out the day. Full PK data for gavage vs hydrogel determined that hydrogel would be used for the 30-day treatment, from 5 - 6 months of age. This long-term study is still underway scheduled to be finished within a month. For both the 7- and 30-day treatments, indirect target engagement was determined by significant increases in the expression of ABCA1 for both Bex and LG268, in E3FAD and E4FAD mice.

Preliminary results from the 7-day study indicate that there was no change in apoE levels. Interestingly, total soluble A β decreased in E4FAD and increased in E3FAD mice. However, oA β levels remained greater in E4FAD compared to E3FAD. In addition, insoluble A β (formic acid extracted) increased with Bex treatment only in the E4FAD mice. Thus, as with the other studies published subsequent to Cramer et al, any changes in A β accumulation, soluble or insoluble/plaque, do not appear to be the result of changes in the level of apoE expression.

Steven Paul, MD, Weill Medical College of Cornell University



Steven M. Paul, MD, is the Director of the Helen and Robert Appel Alzheimer's Disease Research Institute and the Burton P. and Judith B. Resnick Distinguished Professor in Neurodegenerative Diseases. Dr. Paul is also a DeWitt Senior Scholar and Professor of Neuroscience, Brain and Mind Research Institute, Psychiatry and Pharmacology at Weill Cornell Medical College. He was formerly the Executive Vice President of Science and Technology and President of the Lilly Research Laboratories (LRL) of Eli Lilly and Company. Prior to assuming his position at Lilly and Weill Cornell Medical College, Dr. Paul served as Scientific Director of the National Institute of Mental Health (NIMH/NIH) in Bethesda, Maryland.

Dr. Paul is a member of various professional and honorary societies, including Phi Eta Sigma; Alpha Epsilon Delta; Sigma Xi; Phi Beta Kappa; and the Alpha Omega Alpha Honorary Medical Society. He is the recipient of many honors and scientific recognitions, including: The Distinguished Service Medal of the USPHS and the Chief Scientific Officer of the Year Award. In 1997, Dr. Paul was elected to membership in the Institute of Medicine (IOM) of the National Academy of Sciences and currently serves on the IOM's Board on Health Sciences Policy. In 2009 Dr. Paul was elected a Fellow of the American Association for the Advancement of Science (AAAS). Dr. Paul has authored or co-authored over 500 papers and invited book chapters and was listed as one of the most highly cited scientists in the world (top 50 in Neuroscience) (1980-2000) by the Institute for Scientific Information (I.S.I.), Philadelphia, Pennsylvania. He holds 9 patents on inventions made both at NIH and Lilly. His current work has focused on the role of apoE in the pathogenesis of Alzheimer's disease. He is also an inventor of solanezumab, a humanized anti-A β monoclonal antibody currently in late-stage clinical testing by Lilly as a potential disease-modifying treatment for Alzheimer's disease. Dr. Paul is on the boards of several publicly traded and private biopharmaceutical companies and is a founder of two start-up biotechnology companies dedicated to discovering and developing novel psychiatric drugs, including drugs for mood and psychiatric disorders.

Gene Delivery of Apolipoprotein E2 as a Treatment for Alzheimer's Disease

Steven Paul

Appel Alzheimer's Disease Research Institute, Weill Medical College of Cornell University, New York, NY, USA

The apoE4 allele is a well-established genetic risk factor for late-onset AD, where homozygotes have a >15-fold greater risk of developing AD and also develop the disease approximately a decade earlier than apoE3 homozygotes. By contrast, the apoE2 allele is protective, reducing the risk of developing AD by approximately 50% and markedly delaying disease onset. Understanding how these two apoE alleles so dramatically alter the risk of developing AD is an important goal of contemporary AD research. Work in my laboratory employing transgenic mouse models of AD have demonstrated a profound impact of the three apoE isoforms on brain A β /amyloid burden (E4>E3>E2) and clearance (*J. Neurosci.*,29(21),6771-6779, 2009). However, the cellular and molecular mechanisms underlying apoE's effect on A β clearance and brain A β /amyloid burden are still poorly understood. Based on the robust protective effect of the apoE2 allele on AD risk, we have previously administered apoE2 directly into the hippocampus of our PDAPP transgenic mouse model of AD using viral-mediated gene delivery and observed a rapid and robust reduction in brain amyloid burden and neuritic plaques (*Proc. Natl Acad. Sci.* 102, 1211-1216, 2005). Excellent expression of apoE2 for well over 12 months in the mouse brain was readily achieved using this lentiviral vector. Given these striking findings and our unpublished data demonstrating that intraventricular administration of this lentiviral apoE2 vector results in apoE2 expression in the choroid plexus and ependymal cell lining of the ventricle with widespread brain levels of apoE protein, we now propose to advance gene delivery of apoE2 as a potential therapeutic strategy for AD. To accomplish this we have switched from using lentivirus to deliver apoE2 via direct intracerebral administration to exploring a series of adenoassociated viral (AAV) vectors (of different serotypes), cell-specific promoters and several routes of administration (including intracisternal/intrathecal administration) to optimize the level of brain expression in a new mouse model of apoE4-dependent amyloid deposition/AD pathology. In this presentation I will review the rationale for this therapeutic strategy as well as our preliminary results using AAV-mediated gene delivery of apoE2 to alter amyloid pathology in both PDAPP mice as well as this new mouse model of AD. Future studies in transgenic mice and nonhuman primates will be carried out to support possible clinical trials of our apoE2 gene therapy protocol in subjects at high risk to develop AD.

Steven Estus, PhD, University of Kentucky Research Foundation



Steve Estus earned his PhD in Pharmacology at Case Western Reserve University. After post-doctoral fellowships on APP processing with Steve Younkin and neuronal apoptosis with Gene Johnson, he joined the University of Kentucky where he is currently Professor and Vice-Chairman in Physiology. His work is facilitated by his association with the Sanders-Brown Center on Aging and Alzheimer's Disease Center. His laboratory seeks to elucidate the molecular mechanisms underlying Alzheimer's disease, with a particular focus on the role of gene expression and RNA splicing in the actions of genetic polymorphisms that modulate Alzheimer's risk.

CSF Levels of apoE and apoJ Complexes with A β

Steven Estus

University of Kentucky Research Foundation, Lexington, KY, USA

To evaluate the hypothesis that increased levels and lipidation of apolipoprotein E (apoE) and apolipoprotein J (apoJ, clusterin) in CSF will enhance complex formation with A β we have developed novel ELISAs to quantify apoE/A β and apoJ/A β complexes. We will additionally test the sub-hypothesis that these complexes serve as CSF biomarkers for AD. Complex levels will be evaluated as a function of AD status, the presence of *APOE4*, and sex in well-characterized human CSF samples. Read-outs will include the levels apoE, apoJ, apoE/A β and apoJ/A β , as well A β 40, A β 42, p-tau and tau. We will also analyze the extent that complex levels are altered by treatment with valproic acid (VPA). This analysis is based on preliminary results, including (i) the AD-protective alleles of *CLU* (*APOJ*) and *ABCA7* are associated with modest but significant increases *in vivo* in the expression of *CLU* and *ABCA7*, the latter of which may enhance apoE and apoJ lipidation and (ii) VPA increases *CLU* and *ABCA7* expression *in vitro*. Overall, this two-pronged study will evaluate (i) the utility of apoE/A β and apoJ/A β complexes as AD biomarkers and (ii) the repurposing potential of VPA as an AD preventative by evaluating VPA effects on endpoint targets derived directly from genetic studies.

Tae-Wan Kim, PhD, Columbia University Medical Center



Tae-Wan Kim obtained his undergraduate degree from Yonsei University, Seoul, Korea, and received his PhD in neurobiology under the supervision of the late Ira Black from Rutgers University, New Jersey, USA. Following postdoctoral training with Dr. Rudy Tanzi at the Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA, he held faculty appointments at Harvard Medical School and Columbia University. He is currently an Associate Professor in the Department of Pathology and Cell biology and in the Taub Institute at Columbia University. His previous research has focused on the molecular mechanism underlying familial Alzheimer's disease (AD) with emphasis on the pathobiology of presenilins, as well as the

role of bioactive lipids (e.g. phosphoinositides) in AD. For the past several years, his research expanded to seek new targets and pathways involved with AD using the combined approaches of unbiased phenotypic compound screening relevant to AD and the use of physiological neurons derived from stem cells.

Development of Screening Assays for Tauopathy in Stem Cell Derived Neurons

Tae-Wan Kim

Columbia University Medical Center, New York, NY, USA

Owing to the chronic, complex and heterogeneous nature of neurodegenerative diseases such as Alzheimer's disease (AD), a target-directed drug discovery approach, although conceptually rational, has resulted in limited success. Phenotypic drug discovery (PDD), however, offers a complementary approach to conventional target-based drug discovery. To establish phenotypic PDD screening relevant to AD, a cell-based model that recapitulates physiological properties of the target neuronal population carries significant value in discovering improved drug candidates and chemical probes for uncovering disease mechanisms. To this end, we recently reported phenotypic neuronal assays for biogenesis and synaptic action of amyloid β -peptide ($A\beta$) based on embryonic stem (ES) cell-derived neurons (ESNs) originated from a mouse model of AD. ESNs enriched with pyramidal neurons (a neuronal population mainly affected in AD brain) were robust, scalable and amenable to a high throughput screening (HTS) assay, overcoming apparent limitations of neuronal models derived from human pluripotent cells. In our current study, we are establishing HTS assays and performing small molecule screening to identify compounds that can reduce tau protein levels. The levels of tau are critically associated with susceptibility of neurons to $A\beta$ -induced synaptotoxicity, based on observations that the deletion of tau (*MAPT*^{-/-}) leads to the full rescue of learning and memory deficits found in mouse models of β -amyloidosis. Our approach has the potential to yield a number of interesting bioactive compounds that can modulate tau via novel mechanisms, and be further developed as therapeutic small molecules for AD and other neurodegenerative diseases associated with tauopathies.

Li Huang, PhD, Duke University



Dr. Li Huang is an assistant professor in the Department of Surgery, Duke University Medical Center. She completed her PhD at the University of North Carolina-CH and postdoctoral studies at Research Triangle Institute (RTP, NC) and Vanderbilt University (Nashville, TN). Her research in the last ten years has been focused on studies of natural product-derived small molecules as potential therapeutics against pathogens and diseases including HIV-1, influenza viruses, cancer, and neurodegeneration.

Proteasome Activators as Drug Candidates for Alzheimer's Disease

Li Huang

Duke University, Durham, NC, USA

There has been an increase in evidence suggesting that impairment in the clearance of phosphorylated tau (p-tau) and beta-amyloid peptides is associated with Alzheimer's disease (AD). Therefore, improving the clearance of beta-amyloid and p-tau could be an attractive strategy against AD progression. The proteasome is one of the cellular machineries involved in beta-amyloid degradation and tau protein turn over. The proteasome function can be inhibited by beta-amyloid and thereby worsen the accumulation of beta-amyloid and p-tau. Therefore, our goal is to identify small molecule proteasome activators that promote the clearance of the abnormal protein aggregates, including beta-amyloid and p-tau. As a step toward this goal, several structural diverse molecules that can activate the proteolytic activity of the proteasome have been identified. Further chemical modifications based on these hits have led to the discovery of two lithocholic acid derivatives 3 α -O-pimeloyl-lithocholic acid methyl ester (1) and its 3-N-isosteric isomer (2) that can potently activate the proteasome. Unlike the cellular proteasome activator PA28, the proteasome that activated by compound 1, was not inhibited by beta-amyloid. Furthermore, compound 1 potently antagonized the inhibitory effect of beta-amyloid on PA28-activated proteasome. Our preliminary results also indicate that compound 1 facilitates the clearance of p-tau using a neuroblastoma cell model. In summary, we have discovered several classes of small molecule proteasome activators. The ability of these proteasome activators to facilitate the clearance of beta-amyloid and p-tau warrants further study to determine their potential as drug candidates for AD.

Wai Haung Yu, PhD, Columbia University Medical Center



Wai Haung (Ho) Yu received his PhD from the University of Toronto (Pharmacology) in 2001. While at the University of Toronto, he was recipient of several fellowships including the Alzheimer's Society of Canada Doctoral fellowship, University of Toronto Open Scholarship for Graduate Studies and the inaugural Theodore I. Sherman Graduate Award in Neuroscience. Following his PhD, he went to New York University/Nathan Kline Institute where he did his post-doctoral work with Dr. Ralph (Randy) A. Nixon. During this time, he held a Canadian Institutes of Health Post-doctoral fellowship and produced work on the role of autophagy in Alzheimer's disease that is now considered seminal in the field. Dr. Yu was promoted to Clinical Instructor and

then Assistant Professor at NYU prior to his move to Columbia University where he continues his work on autophagy in AD and PD, with an emphasis of the translational outcome of modulating autophagic and lysosomal degradation in neurons. Dr. Yu serves on several Review Boards including the W. Garfield Weston Foundation, Alzheimer Drug Discovery Foundation and the Veteran's Administration. Dr. Yu also serves as President of the Greater NYC Chapter for the Society for Neuroscience, whose Outreach volunteers were awarded the Next Generation Prize in 2011. This Outreach program continues to expand and promote neuroscience education for the public.

Enhancement of Autophagy and Clearance of Tau

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Protein quality control is an essential function for cellular viability. The bulk of this process is mediated by the ubiquitin-proteasome system (UPS) and the autophagic-lysosomal system (A-LS). While the UPS clears mostly soluble proteins, A-LS is responsible for the clearance of dysfunctional organelles and redundant proteins in both soluble and aggregated forms. A common pathological hallmark in all neurodegenerative diseases is the aggregation of proteins, which is often linked to a loss of protein quality control. Tauopathies are one collection of neuropathological disorders encompassing over two dozen neurodegenerative diseases, all associated with the accumulation of the microtubule associated protein, tau. This spectrum of disorders includes Alzheimer's disease and a large proportion of frontotemporal dementia (FTD) and Parkinsonism cases. Although constitutive A-LS activity is robust, there is evidence that it is insufficient to maintain sufficient protein quality control, especially at latter stages of the neuropathological process. Autophagy can also be induced and this work investigates the activation of autophagy through small molecules and test whether these compounds promote the autophagic flux required to clear tau aggregates. This presentation will discuss work on how autophagic induction can promote tau clearance and the development of a new generation of molecules that promote autophagy.

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