Celebrating its 10th Anniversary,
the Alzheimer's Drug Discovery Foundation presents

THE 10TH INTERNATIONAL CONFERENCE ON ALZHEIMER'S DRUG DISCOVERY

September 14-15, 2009

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 10th International Conference on Alzheimer's Drug Discovery.

This meeting brings together academic and industry scientists with an intended mission of accelerating the development of novel drug discovery programs for Alzheimer's disease. Four stimulating sessions spanning over two days will offer updates on ongoing research as well as highlight new studies and concepts.

The three aims of the meeting are multi-dimensional and link discussions on scientific progress of drug discovery programs aimed at Alzheimer's disease with networking opportunities for scientists to share information and resources. Finally, the publication and distribution of a post-meeting report in a peer-reviewed scientific journal brings the exciting developments of the conference to a wider audience.

We have an impressive lineup of presentations and most distinguished lecturers from academia and industry. In addition to sessions focused on neuroprotection and targeting plaques and tangles, this year's agenda includes a new session on alternative strategies for Alzheimer's disease treatment. I am also pleased to note the growing interest and participation of young investigators as they are critical to the future of our field.

This meeting is made possible by the generous support of our many sponsors and exhibitors highlighted on the following pages. I would also like to take this opportunity to extend my sincere appreciation to the chairs and speakers for their tireless efforts in organizing what promises to be a very exciting conference.

As this is an annual event for our Foundation, we hope you will use the attached survey to provide us with your feedback and help us plan an even better conference for 2010!

My hope is that all participants will leave this conference with added knowledge and new prospects for future collaborations. Once again, welcome to the 10th International Conference on Alzheimer's Drug Discovery!

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

ABOUT ADDF

MISSION

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

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

ADDF has an impressive track record of selecting and supporting excellent Alzheimer's disease drug discovery research. Our scientists have created entirely new classes of drugs in development for AD, screened millions of compounds, identified hundreds of leads, executed tens of patents and licenses, and have advanced compounds into clinical trials. To date, we have awarded over $35M for more than 240 research programs and conferences worldwide.

OUR CONFERENCES

ADDF organizes two international scientific conferences yearly 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 Fall, focuses on the discovery and development of drugs targeting Alzheimer's disease and related dementias. The *Drug Discovery for Neurodegeneration* conference, held in winter, is designed to educate scientists on the process of translating basic neuroscience research into innovative therapies. ADDF also plans smaller "catalyst conferences" that center around a relevant topic in the field of neurodegeneration.

PROGRAM

Monday, September 14	
7:30–8:30 am	**Registration & Continental Breakfast**
8:30–8:45	**Welcome & Opening Remarks -** Howard Fillit, MD, Executive Director, Alzheimer's Drug Discovery Foundation
8:45– 9:15	**Plenary: Bridging Neurocognitive Aging and Disease Modification: Targeting Functional Mechanisms of Impairment –** Michela Gallagher, PhD, Johns Hopkins University
I. NEUROPROTECTION STRATEGIES - Chair: Frank Longo, MD, PhD, Stanford University	
9:15–9:20	**Session Overview – Frank Longo, MD, PhD, Stanford University**
9:20–9:40	**BDNF Small Molecule Mimetics for the Treatment of AD -** Frank M. Longo, MD, PhD, Stanford University
9:40–9:50	Q&A
9:50–10:10	**Cognitive and Cardiovascular Benefits of DHA in Aging and Cognitive Decline -** Karin A. Yurko-Mauro, PhD, Martek Biosciences Corporation
10:10–10:20	Q&A
10:20–10:35	**BREAK**
10:35–10:55	**Effects of PPAR-Sparing Thiazolidinediones (TZDs) In TgAPP Mice -** Jerry Colca, PhD, Metabolic Solutions Development Company
10:55–11:05	Q&A
11:05–11:25	**Multiphosphatase Inhibitors in AD -** Asa Abeliovich, MD, PhD, Columbia University
11:25–11:35	Q&A
11:35–11:55	**Efficacy of Herbal extract, Tetramethylpyrazine, in Alzheimer's Transgenic Mice -** Zhiqun Tan, MD, PhD, UC Irvine
11:55 am–12:05 pm	Q&A
12:05–12:25	**Disaggregation of Tau as a Therapeutic Approach to Tauopathies -** Karen Duff, PhD, Columbia University
12:25–12:35	Q&A
12:35–1:30	**LUNCH**
II. ANTI-AMYLOID & PROTEIN MISFOLDING - Chair: Michael Wolfe, PhD, Harvard University	
1:30–1:35	**Session Overview – Michael Wolfe, PhD, Harvard Medical School**
1:35–1:55	**Discovery Of Potent Notch-Sparing γ-Secretase Inhibitors -** Michael Wolfe, PhD, Harvard Medical School
1:55–2:05	Q&A
2:05–2:25	**New Methods to Explore Marine Resources for Alzheimer's Disease -** Philip Williams, PhD, University of Hawaii at Manoa
2:25–2:35	Q&A
2:35–2:55	**Investigation of the Role of SEP in Controlling Cerebral Beta-Amyloid Pathology -** Robert Marr, PhD, Rosalind Franklin University of Medicine and Science
2:55–3:05	Q&A
3:05–3:20	**BREAK**
3:20–3:40	**Fibrinogen, a Possible Key Player in Alzheimer's Disease -** Sidney Strickland, PhD, Rockefeller University
3:40–3:50	Q&A
3:50–4:10	**Targeted Hydrolysis of Beta-Amyloid with Engineered Antibody Fragments -** Michael Sierks, PhD, Arizona State University
4:10–4:20	Q&A
4:20–4:40	**Enhancing Activity Of IDE Through Action Of Small Molecules -** Walter K. Schmidt, PhD, University of Georgia
4:40–4:50	Q&A

4:50–5:10	**Betasynuclein Derived Peptide Sequences for Treatment of AD: Efficacy of a Peptidomimetic Compound in a Transgenic Mouse Model of AD -** Manfred Windisch, PhD, JSW Research
5:10–5:20	Q&A
5:20–5:25	**Closing Remarks -** Diana Shineman, PhD, Alzheimer's Drug Discovery Foundation
5:30–7:00	**NETWORKING RECEPTION**
Tuesday, September 15	
8:15–9:00 am	**Continental Breakfast**
9:00–9:30	**Plenary: Amyotrophic Lateral Sclerosis And Frontotemporal Lobar Degeneration: Connecting The Dots Through TDP-43** - Virginia M.–Y. Lee, PhD, MBA, University of Pennsylvania
III. ANTI-TANGLES & FRONTOTEMPORAL DEMENTIA - Chair: Jeff Kuret, PhD, Ohio State University	
9:30–9:35	**Session Overview – Jeff Kuret, PhD, Ohio State University**
9:35–9:55	**Imaging Agents for Pre-mortem Diagnosis and Staging of Tauopathies -** Jeff Kuret, PhD, Ohio State University College of Medicine
9:55–10:05	Q&A
10:05–10:25	**Hsp90 Inhibitors in Tauopathies: In vivo Pre-Clinical Development -** Gabriela Chiosis, PhD, Memorial Sloan-Kettering Cancer Center
10:25–10:35	Q&A
10:35–11:50	**BREAK**
10:50–11:10	**Clearance of Pathological Tau Confomers -** Einar M. Sigurdsson, PhD, New York University College of Medicine
11:10–11:20	Q&A
11:20–11:40	**Novel Approaches for Targeting Tau Oligomers** – James Moe, PhD, MBA, Oligomerix, Inc.
11:40–11:50	Q&A
11:50 –12:50	**LUNCH**
IV. ALTERNATIVE STRATEGIES: NEW TARGETS FOR AD THERAPY - Chair: Diana Shineman, PhD, ADDF	
12:50–12:55	**Session Overview – Diana Shineman, PhD, ADDF**
12:55–1:15	**PDE9: A New Target for Alzheimer's Disease –** Rebecca M. Evans, MD, MSc, Pfizer
1:15–1:25	Q&A
1:25–1:45	**Small Molecule Agonists of Phosphatidylinositol 4-Kinase as Potential Therapeutic Agents in Alzheimer's Disease –** Tae-Wan Kim, PhD, Columbia University Medical Center
1:45–1:55	Q&A
1:55–2:15	**Peptidomimetics for Elimination of Cofilin Pathology in Alzheimer's Disease -** James R. Bamburg, PhD, Colorado State University
2:15–2:25	Q&A
2:25–2:45	**Use of mGluR5 Inhibitors to Modulate Aβ Production, Accumulation And Signaling In Mouse Models Of AD -** James S. Malter, MD, University of Wisconsin at Madison
2:45–2:55	Q&A
2:55–3:10	**BREAK**
3:10–3:30	**Expedient and Versatile Methods for the Production of Investigational Drugs for SPECT and PET Imaging of AD -** Graham Jones, PhD, Northeastern University
3:30–3:40	Q&A
3:40–4:00	**Novel Approach to Enhance Cognition through the Dopamine D1 Receptor System by Inhibition of PDE1B-** Lawrence P. Wennogle, PhD, Intra-Cellular Therapies, Inc.
4:00–4:10	Q&A
4:10–4:20	**Closing Remarks -** Howard Fillit, MD, Alzheimer's Drug Discovery Foundation

2009 ADDF YOUNG INVESTIGATOR SCHOLARSHIP RECIPIENTS

Congratulations to the winners of the 2009 **ADDF Young Investigator Scholarships!** These highly prestigious Scholarships recognize the early achievements of talented young investigators and seek to encourage the career development of the next generation of research scientists. In addition to individual recognition, the Scholarships honor the organizations responsible for creating and preserving an environment conducive to profound research accomplishment.

Hyung J. Ahn, *Rockefeller University*

Shanta P. Boddapati, *Arizona State University*

Erin E. Congdon, *Columbia University*

Tao Ma, *Weill Cornell Medical College*

Angela McKoy, *Princeton University*

Boobalan Pachaiyappan, *University of Illinois at Chicago*

James Soper, *University of Pennsylvania*

Akina Hoshino, *University of Maryland, Baltimore*

Joyonna C. Gamble-George, *Meharry Medical College*

Ritu Tomar, *Hubrecht Institute*

Our congratulations to our winners and thanks to all applicants of this year's scholarship competition.

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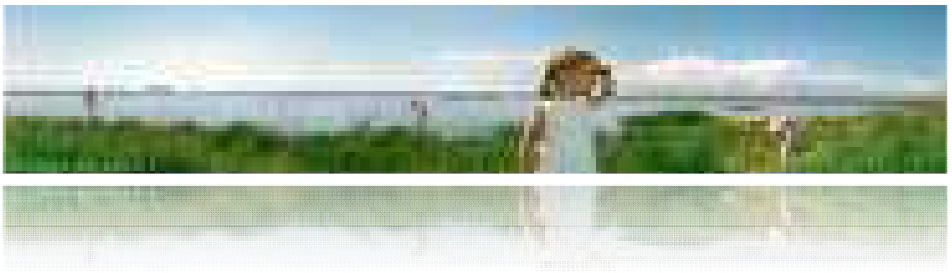

CONFERENCE CHAIR:

Howard Fillit, MD, Alzheimer's Drug Discovery Foundation

Dr. Fillit, a geriatrician and neuroscientist, is the founding Executive Director of the Institute for the Study of Aging, Inc. as well as its affiliated public charity the Alzheimer's Drug Discovery Foundation, both of which are dedicated to funding drug discovery for Alzheimer's disease.

Dr. Fillit was formally the Corporate Medical Director for Medicare at NYLCare Health Plans (now a division of Aetna, Inc.), where he was responsible for over 125,000 Medicare members in 8 regional markets. He has also had a distinguished academic career at The Rockefeller University and The Mount Sinai Medical Center (NY), where he is currently a clinical professor of geriatrics and medicine and a professor of neurobiology.

Dr. Fillit has received many awards and honors, including the Rita Hayworth Award for Lifetime Achievement from the Alzheimer's Association. He is a fellow of the American Geriatrics Society, the American College of Physicians, the Gerontological Society of America, and the New York Academy of Medicine.

Dr. Fillit is the author or co-author of more than 250 publications, including the leading international Textbook of Geriatric Medicine and Gerontology. He served as a consultant to a variety of individuals, managed care organizations, health care systems, and pharmaceutical and biotechnology companies.

Michela Gallagher, PhD, Johns Hopkins University

Dr. Michela Gallagher received her B.A. from Colgate University in 1969 and Ph.D. from The University of Vermont in 1977. She rose through the faculty ranks at University of North Carolina at Chapel Hill, where she was the Kenan Professor of Psychology prior to joining Johns Hopkins University in 1997.

She has published over 150 peer-reviewed papers, has been the recipient of a Senior Research Scientist Award from NIMH (1990-1999), a Freedom to Discover Award from the Bristol-Myers Foundation (2003-2008), and Senior Scientist Award from the Ellison Medical Foundation (2008-2012). She is a fellow of the American Psychological Association, the American Psychological Society, and the American Association for the Advancement of Science. She chaired the Department of Psychological and Brain Sciences at Johns Hopkins from 2000-2007.

Dr. Gallagher now serves as the Director of the Neurogenetics and Behavior Center at Johns Hopkins University and heads a multi-institutional research program funded by the National Institute on Aging. Her scientific work established a model for neurocognitive aging that shifted research from studies of neurodegeneration as a cause of memory loss to uncovering functional mechanisms. She currently serves part-time as the Vice Provost for Academic Affairs at Johns Hopkins.

PLENARY PRESENTATION:

BRIDGING NEUROCOGNITIVE AGING AND DISEASE MODIFICATION: TARGETING FUNCTIONAL MECHANISMS OF IMPAIRMENT

Michela Gallagher
Johns Hopkins University

Basic research, leading to fundamental discoveries on the complex molecular pathways underlying the pathophysiology of Alzheimer's disease, has opened the way to promising targets for interventions and therapies. Much parallel progress is being made in the field of cognitive neuroscience in understanding the essential circuits for memory. Because effective therapy for AD will ultimately be measured by the response of the patient's clinical condition, studies of mild cognitive impairment, grounded in the knowledge of cognitive neuroscience, give important clues about the basis for memory loss that can inform the effort to bridge from molecules and preclinical models to the earliest clinical symptoms in Alzheimer's disease. From this perspective the concept that altered network properties underlying memory loss also drive pathology suggests a novel entry point for early intervention.

I. NEUROPROTECTION STRATEGIES - Chair: Frank Longo, MD, PhD, Stanford University

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BDNF Small Molecule Mimetics for the Treatment of Alzheimer's Disease - Frank Longo, MD, PhD, Stanford University

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Multiphosphatase Inhibitors in AD - Asa Abeliovich, MD, PhD, Columbia University

Efficacy of Herbal Extract, Tetramethylpyrazine, in Alzheimer's Transgenic Mice - Zhiqun Tan, MD, PhD, University of California Irvine

Disaggregation of Tau as a Therapeutic Approach to Tauopathies - Karen Duff, PhD, Columbia University

Frank M. Longo, MD, PhD, Stanford University

Dr. Longo received his MD in 1981 and PhD in Neurosciences in 1983 from the University of California, San Diego. Following an internship in medicine at NYU/VA, he trained as a resident in neurology and fellow in neurobiology at University of California, San Francisco. While at UCSF he created the Neurogenetics Clinic which was the first West Coast site in the U.S. to offer DNA testing for families with Huntington's disease. He also led the creation of a national referral center for deep brain stimulation for Parkinson's disease and contributed to the development of programs in dementia, epilepsy and other areas. At UCSF he became professor and vice chair of the Department of Neurology and in 2001 he was recruited to become chair of the Department of Neurology at the University of North Carolina, Chapel Hill. While at UNC, Dr. Longo launched or expanded programs for Alzheimer's disease and other dementias, stroke, epilepsy, sleep disorders, multiple sclerosis and Parkinson's disease. In January 2006, Dr. Longo became chair of the Department of Neurology and Neurological Sciences at Stanford where he is focused on building and expanding multidisciplinary programs in neurology and neuroscience. In 2006 he was named a Stanford Fellow.

Dr. Longo's research team focuses on elucidating novel mechanisms that prevent neural degeneration and promote regeneration. He and his colleagues have pioneered the development of small, drug-like, molecules that target neurotrophin receptors to delay onset of or slow progression of Alzheimer's and other neurodegenerative disorders.

BDNF SMALL MOLECULE MIMETICS FOR THE TREATMENT OF ALZHEIMER'S DISEASE

Frank M. Longo
Stanford University

Through its interaction with the TrkB receptor, BDNF stimulates a number of intracellular signaling pathways that can potentially modify a number of Alzheimer's disease-relevant mechanisms. Recent *in vitro* and *in vivo* studies suggest that BDNF can prevent amyloid-beta (Aβ)-induced neural degeneration. Using the approach of *in silico* screening of small molecule libraries, Drs. Frank Longo (while at UNC) and Stephen Massa (UCSF) designed pharmacophores based on targeted BDNF domains to identify small molecules mimicking BDNF domains. A number of compounds have been identified that bind to TrkB, activate TrkB signaling with high potency and specificity and demonstrate BDNF-like neurotrophic activity. These small molecules prevent Aβ-induced neural degeneration *in vitro* and achieve BDNF-like signaling and neurotrophic effects *in vivo*.

Karin A. Yurko-Mauro, PhD, Martek Biosciences Corporation

Dr Yurko-Mauro is the Associate Director of Clinical Research with Martek Biosciences Corporation. She has sixteen years of clinical and research experience including the development of drugs, biologics, nutritionals, and the evaluation of potential technologies. In her current position at Martek, she leads the Aging and Dementia program in the Clinical Research Department, developing and managing clinical studies and regulatory strategies for Martek's products, DHA and ARA. Prior to joining Martek, Karin was a Senior Clinical Scientist at Cato Research, an international CRO for 7 years. As project leader for a Phase 2b clinical trial in acute ischemic stroke, Karin managed a large international project team from study inception to final study report. Karin has worked on clinical and regulatory project teams in the therapeutic areas of neurology, cardio-vascular disease, pediatric pulmonology, immunology and nutritionals. Her professional experience is supported by graduate and postdoctoral training in pharmacology, neurochemistry, and protein chemistry. Karin obtained her Ph.D. in Pharmacology at the Medical College of Pennsylvania, Philadelphia, PA. Karin received postdoctoral training at the Alfred I. DuPont Institute of the Nemours Foundation, and the NICHD, NIH. Karin also completed a Masters degree in Neuroscience at the University of Harford, Hartford, CT. During her postdoctoral training, Karin obtained a fellowship research grant from the Cystic Fibrosis Foundation examining regulation of the CFTR signal transduction pathways and was awarded an IRTA fellowship at NIH. She has several publications and presentations and has co-authored a book chapter on clinical protocols in "Expediting Drug and Biologics Development: A Strategic Approach", Linberg SE, ed.

COGNITIVE AND CARDIOVASCULAR BENEFITS OF DHA IN AGING AND COGNITIVE DECLINE

Karin Yurko-Mauro, Deanna McCarthy, Edward B. Nelson, Alan Ryan, Norman Salem, Jr., Columbia, MD; Andrew Blackwell, Cambridge, UK and the MIDAS investigators

Docosahexaenoic acid (DHA), the principle omega-3 fatty acid in brain and heart, plays an important role in neural and cardiac function. Memory loss is a prominent health concern, second only to heart disease for older individuals. Decreases in plasma DHA are associated with cognitive decline in healthy elderly and Alzheimer's patients. Higher DHA intake and plasma levels are inversely correlated with an increased relative risk of Alzheimer's disease (AD) and fatal coronary heart disease. DHA supplementation provides well known cardiovascular benefits such as lowering of triglycerides, raising HDL cholesterol, lowering blood pressure and reducing resting heart rate in normal as well as hypertriglyceridemic subjects. A potentially beneficial role for DHA supplementation in preventing or ameliorating cognitive decline with aging is also emerging. In preclinical studies, DHA supplementation restores brain DHA levels and long-term potentiation, improves cerebral blood flow, and enhances learning and memory tasks in aged animals. Dietary administration of algal-DHA also significantly reduces beta amyloid, plaque burden, and tau protein in transgenic AD models. To date, clinical studies with omega-3 fatty acid (DHA+EPA) supplementation have had mixed results with one study in healthy elderly showing no cognitive benefits. Another small study showed improvement with omega-3s on the ADAS-Cog in mild cognitive impairment, but not AD patients. And a trial in mild to moderate AD patients showed no overall omega-3 benefit, however less decline on the MMSE was seen in the least impaired sub-group treated with omega-3s. These trials suggest that early detection and intervention in aging adults with memory problems may be key factors to providing effective therapies. Utilizing this strategy, we recently examined the individual effects of algal DHA clinically as a nutritional neuro-protective supplement for age-related cognitive decline (ARCD). **M**emory **I**mprovement with **DHA S**tudy (MIDAS) was a randomized, double-blind, placebo-controlled, six month study to determine effects of 900mg/d algal DHA on improving cognitive functions (assessed by CANTAB® cognitive battery) in healthy elderly with ARCD. Four hundred eighty-five

subjects with Logical Memory (WMS III) test baseline scores $\geq$1 SD below younger adults were enrolled across 19 US sites. The primary outcome was a change from baseline in CANTAB Paired Associate Learning (PAL), a visuospatial episodic memory test. With a study completion rate of 90%, ITT analysis demonstrated significantly fewer PAL errors with DHA at six months versus placebo (diff. score -1.63±0.76, p=0.03). Delayed Logical Memory was highly associated with the PAL change ($p<0.001$). Verbal Recognition Memory also showed greater DHA immediate and delayed responses ($p<0.02$). Executive function and working memory tests showed no benefit from DHA treatment. Cardiovascular benefit was demonstrated with a significant decrease in resting heart rate in the DHA group ($p<0.03$) which correlated with week 24 plasma levels ($p<0.01$). Blood pressure and body weight remained unchanged between groups. Plasma DHA levels doubled ($p<0.001$) and were correlated with the PAL response ($p<0.04$). Compliance was >82% and the product was well tolerated.
Conclusions: Six month supplementation with 900mg/d algal DHA improves learning and episodic memory functions and decreases heart rate in older adults with ARCD. These results suggest cognitive and cardiovascular benefits of a well tolerated DHA supplement for the aging population.

Jerry R. Colca, PhD, Metabolic Solutions Development Company

Dr. Jerry Colca has more than 30 years of experience in diabetes research. He has a PhD in biochemistry and physiology from the University of Houston, where he studied the regulation of secretion of pancreatic hormones. In his postdoctoral work at Washington University, working with Michael McDaniel and colleagues he studied the biochemistry of isolated pancreatic islets and stimulus-secretion coupling in the control of metabolism. In 1984 he joined the Upjohn Company, where he led a research team that developed pioglitazone hydrochloride (Actos®). He remained a leader in diabetes discovery through several corporate mergers, retiring from Pfizer in 2005. Dr. Colca has published extensively on the mechanism of action of the insulin-sensitizing thiazolidinediones. In January 2006, he co-founded Metabolic Solutions Development Company with Dr. Rolf Kletzien to develop novel therapeutics based on unique mitochondrial actions of insulin sensitizing agents.

EFFECTS OF PPAR-SPARING THIAZOLIDINEDIONES (TZDS) IN TgAPP MICE

Jerry R. Colca[1], Sergey Kalinin[2], and Douglas L. Feinstein[2]
[1]Metabolic Solutions Development Company; [2]University of Illinois at Chicago

Several studies have suggested that TZDs can reduce amyloid burden, neuroinflammation, and learning deficits in transgenic mice (TgAPP mice) expressing familial mutation of amyloid precursor protein (APP) and presenilin 1(PS1), and possibly in AD patients. Thiazolidinediones (TZDs) are best known as agonists of the Peroxisome Proliferator Activated Receptor gamma (PPARγ) transcription factor. Although activation of PPARγ may be responsible for some actions of these compounds, there is growing evidence that suggest that there are mitochondrial targets which may account for many beneficial effects of these drugs. PPAR-sparing TZDs with selective mitochondrial actions that may eliminate dose-limiting side effects such as fluid retention and weight gain are now in development for the treatment of type 2 diabetes. Here we have examined the effects of PPARγ-sparing TZDs in vitro and in vivo to determine if they can reduce inflammation and amyloid burden. A panel of novel TZDs were tested for their ability to inhibit production of nitric oxide from glial cells, activate a PPAR response element (PPRE), and cause cell damage. MSDC-0160, one of the TZDs currently in Phase 2 clinical trials for diabetes, showed the greatest efficacy to reduce nitrite production, with minimal activation of the PPRE and no cytotoxic effects. Oral dosing of this compound resulted in brain levels that were from 35-41% /mg brain tissue as compared to plasma concentration/ml. In preliminary studies, we treated 2 month old female TgAPP mice ("5xFAD" which express APP having 3 mutations, and PS1 having 2 mutations) with varying doses of MSDC-0160 in the chow for 4 weeks, after which we examined brains for amyloid burden and glial inflammation. Treatment with 300 ppm Mitoglitazone (roughly 30 mg / kg daily dose) led to a 20% reduction ($P = 0.07$) in soluble Ab1-42 levels measured by ELISA, and a trend towards reductions (30%) in total GFAP staining. Treatment of older (6 month) female mice with 300 ppm Mitoglitazone also showed a trend towards reducing Ab1-42 levels (25%). Imunohistochemical analysis of brain sections from these mice is underway to determine if amyloid plaques and brain inflammation are reduced. These preliminary findings suggest that a PPARγ-sparing TZD may provide benefit in TgAPP mice and form the basis for ongoing studies that will include measurements of the potential of this treatment to improve cognitive deficits. The mitochondrial target of TZDs may represent a newly identified target for the treatment of AD.

Asa Abeliovich, MD, PhD, Columbia University

Dr. Asa Abeliovich is an Assistant Professor of Pathology at Columbia University. He is also a member of the Center for Neurobiology, the Department of Neurology, and Behavior and the Taub Institute for Alzheimer's Disease and the Aging Brain. Dr. Abeliovich joined the Columbia faculty in 2000. His interest lies in aspects of dopamine neuron development, function, and survival. A particular focus is on the mechanism by which genetic mutations that have been linked to familial forms of Parkinsonism lead to dopamine neuron loss. With respect to development, Dr. Abeliovich uses stem cells, including embryonic stem cells, as simple in vitro clonal cell culture models to dissect the molecular regulation of mammalian dopamine neuron maturation. ES cells can mature in vitro through roughly the same series of developmental events as the more complex in vivo process.

Dr. Abeliovich graduated from MIT with bachelor's degrees in Life Sciences and Humanities, and was then awarded a Medical Scholar Training Program Fellowship at Harvard Medical School. He undertook his thesis research in the laboratory of Dr. Susumu Tonegawa, where he studied molecular mechanisms of learning. He graduated from Harvard/MIT with MD and PhD degrees in 1996 and subsequently completed clinical training in Neurology at UCSF. At Genentech, Inc. (1996-2000), in South San Francisco, he initiated research on mechanisms of dopamine neuron development and survival with Dr. Arnon Rosenthal. Dr. Abeliovich also sees patients in the Memory Disorders Clinic within the Department of Neurology. He was awarded the Lamport award for excellence in basic science research at Columbia University in 2005.

MULTIPHOSPHATASE INHIBITORS IN ALZHEIMER'S DISEASE

Asa Abeliovich
Columbia University

Midbrain dopamine neurons (mDNs) play a central role in complex behaviors such as reward and addiction, and these cells are lost in Parkinson's disease (PD). A number of transcription factors have been implicated in the regulation of mDNs. However, the role of post-transcriptional mechanisms in mDNs, or in other post-mitotic neuron types, is relatively uncharacterized. Here we investigate the role of microRNAs (miRNAs) in mDN regulation, in relation to previously described transcriptional control mechanisms. miRNAs are evolutionarily conserved, 18-25 nucleotide non-protein coding transcripts that play an important function in post-transcriptional regulation of gene expression during development. In preliminary studies and a recent manuscript, we identified 8 miRNA enriched in the midbrain, and one--miR-133b—that functions within a feedback circuit with the homeodomain transcription factor Pitx3.

Zhiqun Tan, MD, PhD, University of California Irvine

Zhiqun Tan, MD, PhD, is an Assistant Professor of Research in the Department of Neurology at University of California Irvine School of Medicine.

He received his M.D. in 1985 from Tongji Medical University, B.Sc. in Biochemistry in 1987 and Ph.D. in Biological Chemistry in 1993 from Wuhan University in China. He then worked as a faculty member at Wuhan University in the field of environmental toxicology. In 1996 he came to the United Stated and trained as a postdoctoral fellow at the University of Southern California Keck School of Medicine.

He joined the faculty at UCI Neurology Department in 2002 and has been studying on neuronal degeneration. His current research focuses on the pathological changes in the eyes during the progression of Alzheimer's disease and identifying effective therapeutic molecules from natural sources for pharmacological interventions.

EFFICACY OF HERBAL EXTRACT, TETRAMETHYLPYRAZINE, IN ALZHEIMER'S TRANSGENIC MICE

Zhiqun Tan
University of California Irvine

Tetramethylpyrazine (TMP), also called as ligustrazine, is an alkaloid originally isolated from the rhizome of the Chinese medicinal herb, *Ligusticum wallichii* Franchat (*chuanxiong*). For hundreds of years, *chuanxiong* has been used as a therapeutic medicine for heart, kidney, and brain diseases by the traditional Chinese medicine practitioners. Experimental evidence indicates that TMP is an anti-inflammatory and antioxidant small molecule with capacity to block cellular calcium influx. Systemic administration of TMP has shown neuroprotective and promoted functional recovery in animal models of ischemia, stroke, spinal cord injury, and glaucoma. However, this naturopathic compound has not been tested in a transgenic mouse model of Alzheimer's disease (AD). Here we reported the efficacy of systemic treatments with TMP in a triple transgenic mouse model of AD (3xTg-AD) that expresses mutant forms of amyloid precursor protein (APP), presenilin 1 (PS1) and tau and develops both beta-amyloid and tau pathologies with significantly increased neuroinflammatory markers in the brain. Both 10- and 16-month old 3xTg-AD mice (females) and 16-month old wild type (WT) mice were fed chow containing TMP (300 mg/Kg). Equivalent numbers of 3xTg-AD and WT littermates for each group were fed identically-sourced chow without TMP and used as controls. After 60-day continuous treatments, animals were tested by the novel object recognition task (NORT) for their short-term memory and Morris water maze (MWM) task for the learning performance. Following MWM, mice were euthanized and both brains and eyes removed for histopathological examinations to analyze the effects of TMP treatments on Alzheimer's pathologies in both brain and retinas. Results demonstrated that both 12- and 18-month old 3xTg-AD mice showed significant deficits in the learning and memory performance as revealed by both NORT and MWM acquisition. In contrast, TMP treatments remarkably improved the cognitive performance in 3xTg-AD mice. Immunohistochemistry showed that TMP treatments efficiently removed beta-amyloid plaques and reduced neuroinflammatory markers in both coronal and cross-retinal sections. Biochemical analysis demonstrates much lower amounts of lipid peroxidation products as well as of oligomeric forms of beta-amyloid in the brain lysates from TMP-treated mice. We conclude that TMP reduces beta-amyloid and neuroinflammatory processes in both brain and retinas and ameliorates cognitive dysfunction in 3xTg-AD mice.

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

Karen Duff, PhD, Columbia University

Dr. Duff received her Ph.D from Sydney Brenner's dept at the University of Cambridge (UK) in 1991. She has held positions at the University of South Florida in Tampa, Mayo Clinic Jacksonville, and the Nathan Kline Institute (NYU) in New York. In 2006 she moved to the Taub Institute at Columbia University and is a tenured Professor in the Pathology Department, with a joint position at the NYS Psychiatric Institute.

The main focus of Dr. Duff's work is to examine mechanisms involved in the development of neurodegenerative diseases (Alzheimer's, Tauopathies etc) and to test therapeutic approaches that may attenuate disease progression. Over the last 20 years, Dr. Duff has used genetic engineering technology to create several mouse models for AD that develop either plaques or tangles. The mice that form amyloid plaques have been especially well used to examine different aspects of AD, from the development of methods for MRI based diagnosis of amyloidosis, to understanding mechanisms by which the brain degenerates. In addition, the mouse models have been used to study how possible therapeutic strategies may help in the treatment, or prevention of AD. Currently, her main interests are in exploring how tangles form in the brain and therapeutic approaches to reduce their impact, and how AD is initiated in Late Onset AD. Dr. Duff has won several prizes for her work, including the Potamkin Prize In 2006. Her CV includes over 100 peer reviewed research articles and she is a regular speaker at scientific meetings around the world. Her work is mainly funded by the NIH and foundations.

DISAGGREGATION OF TAU AS A THERAPEUTIC APPROACH TO TAUOPATHIES

Karen Duff
Columbia University

Neurofibrillary tangles (NFTs) form in the brain of patients with a wide range of dementias of which AD and FTD are the most common. Collectively, diseases with tangle pathology are known as tauopathies. While the etiology of the tauopathies varies, all result in the formation of insoluble, aggregated tau that accumulates in the cell body. Preventing or reversing abnormal tau formation, either in the form of oligomers or more complex aggregates is therefore a worthwhile therapeutic goal. Dr. Jeff Kuret's lab has shown that cyanine dyes are capable of disaggregating and depolymerizing recombinant tau filaments, especially those in an aberrant conformation. We have shown that a cyanine dye can enter cells in a slice culture prepared from a mouse with tauopathy, and can alter the level of insoluble tau that forms in these cultures. Our data shows that there was a biphasic curve for tau disaggregation - at high doses, insoluble tau levels increase whereas at low doses, insoluble tau levels decrease. The change in insoluble tau was not associated with any change in phosphorylation status of the tau. Tau filament length and number were decreased as insoluble tau levels decreased, and the size distribution of filaments remained normally distributed. The compound is not toxic, it enters the cells and, most importantly, it is active on insoluble tau formed under ex vivo conditions. We have recently shown that a second compound that disaggregates tau, methylene blue, also decreases, or increases insoluble tau in a dose-dependent manner. However, p-tau is altered in these cultures suggesting different mechanisms of action. These studies validate this type of approach (aggregation inhibition), and also these classes of compound for future studies.

II. ANTI-AMYLOID & PROTEIN MISFOLDING - Chair: Michael S. Wolfe, PhD, Harvard Medical School

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Selective Amyloid-Lowering Agents - Michael S. Wolfe, PhD, Harvard Medical School

New Methods to Explore Marine Resources for Alzheimer's Disease - Philip Williams, PhD, University of Hawaii at Manoa

Investigation of the Role of SEP in Controlling Cerebral Beta-Amyloid Pathology - Robert A. Marr, PhD, Rosalind Franklin University of Medicine and Science

Interaction between Abeta and Fibrinogen: A New Therapeutic Target for Alzheimer's Disease - Sidney Strickland, PhD, Rockefeller University

Targeted Hydrolysis of Beta-Amyloid with Engineered Antibody Fragments - Michael Sierks, PhD, Arizona State University

Enhancing IDE-mediated Destruction of Abeta and other Amyloidogenic Peptides - Walter K. Schmidt, PhD, University of Georgia

Betasynuclein Derived Peptide Sequences for Treatment of Alzheimer's Disease: Efficacy of a Peptidomimetic Compound in a Transgenic Mouse Model of Alzheimer's Disease - Manfred Windisch, PhD, JSW Lifesciences GmbH

Closing Remarks - Diana Shineman, PhD, Assistant Director of Scientific Programs, Alzheimer's Drug Discovery Foundation

Michael S. Wolfe, PhD, Harvard Medical School

Michael S. Wolfe received his B.S. in chemistry in 1984 from the Philadelphia College of Pharmacy and Science and earned his Ph.D. in medicinal chemistry in 1990 from the University of Kansas. After postdoctoral stints at the University of Kansas (medicinal chemistry) and the NIH (cell biology), he joined the faculty of the University of Tennessee in Memphis in 1994.

In 1999, he became Associate Professor of Neurology at Harvard Medical School, where his work has focused on understanding the molecular basis of Alzheimer's disease and identifying effective approaches for pharmacological intervention.

In 2006, Dr. Wolfe founded the Laboratory for Experimental Alzheimer (LEAD) at Harvard Medical School.

DISCOVERY OF POTENT NOTCH-SPARING γ-SECRETASE INHIBITORS

Michael S. Wolfe
Harvard Medical School

Overwhelming evidence supports a central role for the amyloid β-peptide (Aβ) in the pathogenesis of Alzheimer's disease (AD). Two proteases, the β- and γ-secretases, produce Aβ from its precursor protein APP, and these enzymes are top targets for therapeutic intervention. However, potent inhibitors of β-secretase typically have poor *in vivo* properties, and γ-secretase inhibitors cause serious toxicities due to interference with the Notch signaling pathway. We have been working toward compounds that directly alter γ-secretase activity to reduce Aβ production without affecting the proteolysis of Notch. Using purified enzyme and substrate, we have shown that γ-secretase can be selectively inhibited in this way by naphthyl-substituted γ-aminoketones and γ-aminoalcohols. These early hits, however, suffered from chemical instability and/or poor potency. Iterative design, synthesis and evaluation have led to the discovery of improved Notch-sparing γ-secretase inhibitors with nanomolar potency in biochemical and cellular assays. These compounds are of low molecular weight and are under evaluation for drug-like properties. The discovery and development of these compounds will be discussed.

Philip Williams, PhD, University of Hawaii at Manoa

Dr. Philip Williams received his undergraduate education at the University of Calgary, Canada, and his Ph.D. from the University of Hawaii at Manoa, in 2003. After postdoctoral work at the Scripps Institution of Oceanography in San Diego, California, from 2003-2006, he returned to the University of Hawaii to join the faculty as an assistant professor.

Dr. Williams' lab focuses primarily on the exploration of marine resources for the potential treatments for Alzheimer's disease and developing new methods to streamline the discovery of biological probes from natural sources.

NEW METHODS TO EXPLORE MARINE RESOURCES FOR ALZHEIMER'S DISEASE

Philip Williams
University of Hawaii at Manoa

In the Amyloid Cascade Hypothesis of Alzheimer's disease, formation of neurotoxic polypeptide oligomers is initiated by cleavage of the transmembrane amyloid precursor protein (APP) by the aspartic protease BACE-1. Inhibition of BACE-1 therefore has the potential to reduce indirectly the concentration of neurotoxic polypeptide oligomers.

We recently began screening marine-derived extracts from a variety of sources (invertebrates and cyanobacteria) for inhibitors of this enzyme.

Based on preliminary screens of approximately 200 prefractionated extracts and an equivalent number of pure marine natural products, we have identified several new inhibitors. This presentation will focus on our screening protocol, specifically our efforts to develop a BACE1 homogeneous affinity, along with the isolation and structure determination of the new compounds, and our biological evaluations to date.

Robert A. Marr, PhD, Rosalind Franklin University of Medicine and Science

Dr. Robert A. Marr is an Assistant Professor in the Department of Neuroscience with a secondary appointment in the Center of Stem Cell and Regenerative Medicine (CSCRM) at Rosalind Franklin University of Medicine and Science. He received his BS in applied biochemistry from the University of Guelph in 1994. In 2000 Dr. Marr obtained his PhD from McMaster University in Hamilton, Canada studying cancer gene therapy. His postdoctoral work at the Salk Institute for Biological Studies in La Jolla, California was primarily on anti-amyloid therapies of Alzheimer's disease.

Dr. Marr joined the faculty at Rosalind Franklin in 2005 and was later cross-appointed with the CSCRM in 2009. His lab primarily studies the role of endopeptidases and apoE in Alzheimer's disease.

INVESTIGATION OF THE ROLE OF SEP IN CONTROLLING CEREBRAL BETA-AMYLOID PATHOLOGY

RA Marr[1], BJ Spencer[2], D Hafez[1], AM Huynh[1], JY Huang[1], AM Bruno[1], E Rockenstein[2], E Masliah[2]
[1]Rosalind Franklin University; [2]University of California San Diego

Proteases that degrade the amyloid-beta peptide (Aβ) are thought to be important in protecting against Alzheimer disease (AD). Understanding these proteases is critical to the understanding of AD and to the development of therapeutic interventions. Of particular interest are endopeptidases that are sensitive to inhibition by thiorphan and phosphoramidon as these inhibitors induce dramatic Aβ accumulation / deposition in rodents. The Aβ degrading enzyme neprilysin (NEP) is the best know target of these inhibitors, however genetic ablation of NEP results in only a modest increase in Aβ levels insufficient to induce plaque deposition even at advanced age. Therefore, we hypothesize there are other endopeptidases targeted by thiorphan and phosphoramidon that are important for Aβ catabolism. NEP2 (aka SEP, NL1, NEPLP, MMEL1/2) is the closest yet identified homolog of NEP, is sensitive to thiorphan and phosphoramidon, and has been shown to degrade Aβ. Therefore, NEP2 may be an important Aβ degrading enzyme. We have found that aged (10 & 14 months) knockout mice deficient for NEP2 or both NEP2 and NEP showed significantly increased Aβ levels. These findings suggest NEP2 cooperates with NEP to control Aβ levels in vivo. These data also imply that NEP2 is a good candidate for AD therapy. NEP2 has been shown to be a more specific Aβ degrading enzyme as it has lower activity against many vasoactive peptides compared to NEP. Therefore, systemic delivery of NEP2 is less likely to produce harmful side effects. Recently, an exciting new technique has been developed which allows for the targeting of apoB-LDL receptor-binding-site tagged (B-tagged) polypeptides across the blood-brain-barrier from the circulation into the brain (Spencer and Verma 2007). We have shown that this method can be used to deliver NEP to the brains of AD-like (APP transgenic) mice resulting in reduced amyloid pathology. Therefore, we have also generated a secreted form of NEP2 and are producing a B-tagged version for in vivo gene therapy.

Sidney Strickland, PhD, Rockefeller University

Sidney Strickland is Professor and Dean of the Graduate School at The Rockefeller University in New York City.

He received his BS in chemistry in 1968 from Rhodes College in Memphis. He obtained his PhD in biochemistry from the University of Michigan in 1972 where he studied the biophysics of enzymology with Vincent Massey. He then was a postdoctoral fellow for two years at Rockefeller with Edward Reich, where he initiated his work on plasminogen activators.

Dr. Strickland joined the faculty of Rockefeller as an Assistant Professor and then Associate Professor. In 1983, he accepted a position as Leading Professor at the State University of New York at Stony Brook. He returned to Rockefeller in 2000 and established the Laboratory of Neurobiology and Genetics. His lab studies mechanisms of neurodegeneration.

FIBRINOGEN, A POSSIBLE KEY PLAYER IN ALZHEIMER'S DISEASE

Marta Cortes-Canteli, Justin Paul, Erin H. Norris, Robert Bronstein, Hyung Jin Ahn, Sidney Strickland
Rockefeller University

Alzheimer's disease (AD) is a complex neurodegenerative disorder characterized by progressive loss of cognitive function and subsequent death. AD patients have an abnormal cerebral vasculature and brain hypoperfusion, and a large body of research, including some from our lab, implicates cerebrovascular dysfunction as a contributing factor to AD. Reducing fibrinogen, a circulating protein critical in hemostasis, provides a significant decrease in the neurovascular damage, blood brain barrier permeability and neuroinflammation present in AD. These studies implicate fibrinogen as a possible contributor to AD.

Michael Sierks, PhD, Arizona State University

Dr. Michael Sierks' research interests center around engineering proteins as tools for studying neurodegenerative diseases. One application is to develop a potential diagnosis and treatment for Alzheimer's Disease (AD), one of the most debilitating diseases affecting the elderly population.

Dr. Sierks is using antibodies to target a protein, b-amyloid, which forms plaque deposits around nerve cells in the brain leading to cell atrophy and death. His laboratory is developing multifunctional antibodies which can both target specific morphologies of b-amyloid and clear it from the brain before it can aggregate into neurotoxic plaques. He is using a similar approach to develop antibodies useful for studying Parkinson's Disease (PD), another debilitating neurological disease. The protein, a-synuclein, forms aggregates or Lewy Bodies inside affected cells of patients with PD. Dr. Sierks is also developing antibodies which can intracellularly target various forms of the a-synuclein protein and inhibit formation of the Lewy Bodies aggregates. These antibodies can be used for in vivo imaging to study the progression of PD, and also as a potential therapeutic.

TARGETED HYDROLYSIS OF BETA-AMYLOID WITH ENGINEERED ANTIBODY FRAGMENTS

Michael Sierks
Arizona State University

Deposition of beta-amyloid (Aβ) is considered an important early event in the pathogenesis of Alzheimer's Disease (AD) and reduction of Aβ levels in the brain can be a viable therapeutic approach. A potentially non-inflammatory approach to facilitate clearance and reduce toxicity is to hydrolyze Aβ at its α-secretase site using single chain antibody fragments (scFvs). We have previously identified an antibody light chain fragment, mk18, that has α-secretase-like catalytic activity. The specific activity of an scFv version of the proteolytic light chain towards Aβ was improved by affinity maturation using yeast surface display. Proteolytic scFvs with improved specificity were selected and shown to prevent aggregation of Aβ in-vitro and reduce Aβ induced cytotoxicity in cell models. The proteolytic scFv can also cleave small soluble oligomeric Aβ which have been implicated as the toxic species in AD, but not large oligomeric species and fibrils. The proteolytic scFvs can be combined with a second scFv to target specific forms and morphologies of Aβ or even APP.

Walter K. Schmidt, PhD, University of Georgia

Walter K. Schmidt is Associate Professor of Biochemistry and Molecular Biology at the University of Georgia.

He holds degrees from Rice University (BA, 1989) and the University of California - Berkeley (PhD, 1995), and trained as a post-doctoral fellow at the Johns Hopkins University School of Medicine.

His laboratory is focused on protease biology, especially as it relates to the disease states of cancer and Alzheimer's disease. The laboratory is specifically investigating the roles of the membrane-bound CaaX proteases and soluble M16A family proteases in the production of isoprenylated proteins. Examples of isoprenylated proteins are the Ras and Ras-related GTPases, Gg subunits, kinases, nuclear lamins, chaperones, and fungal mating pheromones, among many others. The research is supported by federal, state, and private agencies.

ENHANCING ACTIVITY OF IDE THROUGH ACTION OF SMALL MOLECULES

Surya P. Manandhar, Sayali Kukday, Marissa C. Ludley, Benjamin J. Alper, Walter K. Schmidt
University of Georgia

The insulin-degrading enzyme (IDE) cleaves numerous small peptides, including biologically active hormones and disease-related peptides. The propensity of IDE to cleave and neutralize the neurotoxicity of the Abeta peptides, in particular, marks IDE as a potential therapeutic target for Alzheimer's disease. Using a high throughput screening approach and synthetic reporters, we identified small-molecule agents that stimulate rat IDE activity *in vitro*. In certain instances, over three-fold enhanced activity is observed. Intriguingly, several agents appear cell permeable as judged by their ability to enhance IDE activity in a cell-based assay. Correspondingly, the most potent *in vitro* activator induces the most potent cellular effect. The activators we have identified represent new tools for understanding the enzymology of IDE and provide new insight for the future development of small molecule IDE activators as potential AD therapeutics.

Manfred Windisch, PhD, JSW Lifesciences GmbH

Dr. Windisch founded JSW Lifesciences GmbH, an independent international contract research organization located in Grambach, Austria in the year 1999. JSW specializes on research about neurodegenerative disorders and in his current capacity Dr. Windisch focuses on pharmacological studies of novel compounds for treatment AD, PD and stroke, from molecular screening up to in vivo model systems and the design of clinical studies. After graduation from the University of Graz in 1985 he spent several years heading a neurobiology group at the University with research in the field of brain metabolism and animal model development after which he was involved for many years in University and industrial research programs in Europe, North America and Asia. He established a global network of research collaborations and stimulated intensive scientific information exchange. Besides his involvement in research on neurotrophic and neuroprotective factors, he spearheaded several international clinical studies in AD, vascular dementia and ischemic stroke. He is a highly active member of the scientific community and has authored many original research articles in peer-reviewed journals and is organizing conferences in the field of drug development for treatment of neurodegenerative diseases. At the moment his research activities are concentrated on the role of alpha and beta-synuclein in pathogenesis of AD. The main focus is to explore therapeutic possibilities for preventing alpha-synuclein pathology and the interaction with amyloid deposition. He is also active in creating improved models of neurodegenerative diseases, which should allow early drug testing with a higher predictive value. As a member of several scientific advisory boards he is helping to coordinate preclinical and clinical research activities in that field on an international level.

EFFECTS OF BETA-SYNUCLEIN DERIVED PEPTIDOMIMETICS ON HAPP TRANSGENIC MICE

M. Windisch, B. Hutter-Paier, R. Wronski
JSW Lifesciences GmbH

The pathological aggregation of alpha-synuclein can be counteracted by beta-synuclein whereas this activity is restricted to the N-terminal part of the molecule. It has been shown by different laboratories that N-terminal beta-synuclein sequences can also prevent abnormal aggregation of amyloid beta peptides.
After we have tested several beta-synuclein derived peptide sequences in vivo and in vitro, we turned the shortest sequence KEGV into a peptidomimetic compound by synthesising an in retro-inverso peptide using D-amino acids. This compound turned out to be extremely stable, and it exerted in vitro effects comparable to the L-amino acid peptides. We performed an in vivo proof of concept using transgenic mice over-expressing human APP with London and Swedish mutation under the control of Thy-1 promoter. Treatment started at an age of 6 months and was maintained for 3 months with intranasal application of two different dosages of the peptidomimetic compound, of KEGV and of vehicle (PBS) 5 times a week. The treatment resulted in a significant improvement of learning and memory assessed in the Morris Water Maze. This was accompanied by a significant reduction of amyloid plaques in the brain, which was achieved with both the original peptide as well as the peptidomimetic. Effects could be demonstrated in cortex as well as in hippocampus. Reduction and plaque pathology was accompanied by decrease of amyloid peptides in CSF but also a reduction of Abeta 1-40 and Abeta 1-42 in SDS as well as in formic acid fractions isolated from the brain, whereas these peptides were increased in TBS and Triton-X-100 fractions. This indicates that the treatment is increasing the soluble Abeta fraction, most likely as a result of dissolving plaques and other aggregates.
Results in the study are in accordance with previous findings with the original peptide sequences, indicating possible usefulness of the peptidomimetic drug for prevention and treatment of Alzheimer's disease.

Diana Shineman, PhD, Alzheimer's Drug Discovery Foundation

Diana Shineman, PhD, is the Assistant 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 research programs.

Dr. Shineman earned her PhD in Cell and Molecular Biology from the University of Pennsylvania (Penn). At Penn's renowned Center for Neurodegenerative Disease Research led by Drs. Virginia Lee and John Trojanowski, she studied signal transduction pathways that alter amyloid generation in Alzheimer's disease. Dr. Shineman also worked with the Center's Drug Discovery Group to perform high-throughput screening using cell-based assays. In addition to her dissertation research, Dr. Shineman was as an Editorial Intern for the Journal of Clinical Investigation and was an active member of the Penn Biotechnology Group.

Dr. Shineman received a BA in Biology with a Nutrition concentration from Cornell University, where she was named a Howard Hughes Undergraduate Research Scholar. She is also a member of the Society for Neuroscience and an author on numerous peer-reviewed publications.

Virginia M.-Y. Lee, PhD, MBA, University of Pennsylvania

Dr. Virginia M.-Y. Lee is the John H. Ware 3rd Professor in Alzheimer's Research in the Department of Pathology and Laboratory Medicine. She is the Director of the Center for Neurodegenerative Disease Research and Co-director of the Marian S. Ware Alzheimer Drug Discovery Program at the University of Pennsylvania, School of Medicine. She studied music at the Royal Academy of Music in London (1962-1964), obtained a M.S. in Biochemistry from the University of London (1968), and received her Ph.D. in Biochemistry from the University of California at San Francisco in 1973. While a Penn faculty member, Dr. Lee entered the Executive M.B.A. program at the Wharton School of the University of Pennsylvania (1982-1984), and obtained her M.B.A. degree from the Wharton School in 1984. Dr. Lee is the recipient of the Metropolitan Life Foundation Award for Medical Research in Alzheimer's Disease (1991, 1996), the Potamkin Prize for Medical Research in Alzheimer's Disease (1998) and the Bristol-Myers Squibb Biomedical Research Grant in Neuroscience Research (2003).

In 2004 Dr. Lee was appointed a member of the National Advisory Council on Aging (NIH) and elected to membership in the Institute of Medicine of the National Academies in 2005. Dr. Lee's research focuses on the pathogenesis of Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal dementias (FTDs), amyotrophic lateral sclerosis (ALS) and related neurodegenerative disorders of aging.

PLENARY PRESENTATION:

AMYOTROPHIC LATERAL SCLEROSIS AND FRONTOTEMPORAL LOBAR DEGENERATION: CONNECTING THE DOTS THROUGH TDP-43

Virginia M.-Y. Lee
University of Pennsylvania

The disease protein in frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U) and amyotrophic lateral sclerosis (ALS) was identified recently as the TAR DNA-binding protein (TDP-43) thereby providing a molecular link between these two disorders. In FTLD-U and ALS, TDP-43 is redistributed from its normal nuclear localization to form cytoplasmic insoluble aggregates. Moreover, pathological TDP-43 is abnormally ubiquitinated, hyperphosphorylated and N-terminally cleaved to generate C-terminal fragments. Other studies also showed that TDP-43 aggregates are present to variable extent in other neurodegenerative disorders including Alzheimer's and Parkinson's. Furthermore, TDP-43 accumulations are the first non-amyloidogenic aggregates found in any neurodegenerative diseases. This presentation will summarize the rapidly advancing field of TDP-43 proteinopathies.

III. ANTI-TANGLES & FRONTOTEMPORAL DEMENTIA - Chair: Jeff Kuret, PhD, Ohio State University College of Medicine

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Imaging Agents for Premortem Diagnosis and Staging of Tauopathies - Jeff Kuret, PhD, Ohio State University College of Medicine

Hsp90 Inhibitors in Tauopathies: In vivo Pre-Clinical Development - Gabriela Chiosis, PhD, Memorial Sloan-Kettering Cancer Center

Clearance of Pathological Tau Confomers - Einar M. Sigurdsson, PhD, New York University Langone Medical Center

Novel Approaches for Targeting Tau Oligomers – James Moe, PhD, MBA, Oligomerix, Inc.

Jeff Kuret, PhD, Ohio State University College of Medicine

Dr. Kuret is a Professor of Molecular and Cellular Biochemistry at The Ohio State University. He completed his BS degree in biochemistry at the University of California, Los Angeles, and conducted graduate work with Professor Howard Schulman at Stanford University.

After earning his PhD degree in Pharmacology, he joined the laboratory of Sir Philip Cohen in the Medical Sciences Institute, Dundee, Scotland as a postdoctoral fellow, and served on the faculties of Cold Spring Harbor Laboratory and Northwestern University. He currently serves on the Synapse Cytoskeleton and Trafficking (SYN) and Drug Discovery (MNPS-C) review panels at the NIH Center for Scientific Review.

Dr. Kuret's laboratory focuses primarily on tau aggregation and neurofibrillary lesion formation in Alzheimer's disease and frontotemporal lobar degeneration.

IMAGING AGENTS FOR PREMORTEM DIAGNOSIS AND STAGING OF TAUOPATHIES

Jeff Kuret
Ohio State University College of Medicine

Alzheimer's disease (AD) is defined by the appearance of characteristic lesions in the brain. It differs from other neurodegenerative diseases in the protein composition of the lesions and by their hierarchical emergence in distinct brain regions. Thus, the spatial and temporal distributions of pathology can be used to differentially diagnose and stage AD. Neurofibrillary lesions have special utility in this regard. They are composed of tau, a microtubule-associated protein that normally functions in monomeric form to promote tubulin assembly, microtubule stability, and cytoskeletal integrity, but that forms filamentous aggregates in disease. The aggregates selectively bind conformation-sensitive monoclonal antibodies and small molecules such as thioflavine dyes, suggesting that tau-bearing lesions may be detectable with extrinsic probes and hence amenable to whole-brain imaging. Tau-selective probes could have greater utility for pre-mortem diagnosis and staging of AD than β-amyloid directed imaging agents.

Here I will summarize our progress in developing tau-based imaging agents. First, using pharmacokinetic modeling methods, I will describe the molecular properties needed for detection of neurofibrillary lesions in the presence of competing aggregates such as amyloid plaques. Second, using biochemical methods, I will describe the interactions between small molecules and tau aggregates, and commonalities with other cross-β-sheet aggregates. Finally, through pharmacological analysis, I will assess the feasibility of identifying probes with selectivity for tau relative to β-amyloid and α-synuclein.

Gabriela Chiosis, PhD, Memorial Sloan-Kettering Cancer Center

Dr. Gabriela Chiosis is a Principal Investigator in the Program in Molecular Pharmacology and Chemistry at Sloan-Kettering Institute, and an Assistant Attending in the Department of Medicine of Memorial Hospital for Cancer & Allied Diseases, New York. She is also a faculty in several biomedical graduate programs such as the Program in Pharmacology, Weill Graduate School of Medical Sciences, Cornell University, the Tri-Institutional Training Program in Chemical Biology, Sloan-Kettering Institute for Cancer Center, Cornell University and The Rockefeller University and the Cancer Biology Program of the Gerstner Sloan-Kettering Graduate School. She received her graduate training at Columbia University in New York and has joined Memorial Sloan-Kettering Cancer Center in 1998.

The Chiosis Laboratory investigates the significance of modulating molecular chaperones in disease treatment. In this respect, it has developed pharmacological tools instrumental in defining the roles of Hsp90 in regulating the stability and function of aberrant protein driving the neurodegenerative phenotype in tauopathies. Hsp90 inhibitors discovered by the lab are the platform for the development of purine-scaffold Hsp90 inhibitor currently in Phase I evaluation in patients with advanced cancers.

Hsp90 INHIBITORS IN TAUOPATHIES: IN VIVO PRE-CLINICAL DEVELOPMENT

Gabriela Chiosis
Memorial Sloan-Kettering Cancer Center

Hsp90 is a molecular chaperone with important roles in regulating pathogenic transformation. Our laboratory has pioneered the discovery and development of synthetic Hsp90 inhibitors, and identified derivatives with favorable BBB-permeability profile. Administration of these molecules to tau transgenic mice resulted in modulation of aberrant neuronal proteins and a reduction in both toxic tau aggregates without toxicity to the mice. It also led to induction of Hsp70 in pathogenic neurons. In various cellular models of AD, increased levels of Hsp70 promoted tau solubility and tau binding to microtubules. Hsp70 also inhibited the propensity of Aβ to aggregate, and reduced the toxicity of Aβ on neuronal cultures. These observations suggest that in neurodegenerative diseases in general, and AD in particular, Hsp90 inhibition offers a dual therapeutic approach. First, it ameliorates protein misfolding by reduction of aberrant neuronal protein activity that leads to protein hyperphosphorylation and subsequent aggregation. Second, its therapeutic benefit comes from induction of Hsp70, a chaperone able of redirecting neuronal aggregate formation, and of protective potential against both Abeta and tau aggregate toxicity. Based on these data, we propose that Hsp90 inhibitors represent a multifaceted potential novel treatment to extend the survival of afflicted neurons. This talk is part of a large, ongoing effort focused on tailoring the Hsp90 inhibitors through iterative feed-back medicinal chemistry-pharmacology-pharmaceutical profiling to identify an orally available molecule that has optimal BBB-permeability and is efficacious in improving symptoms in AD both at a behavioral and biochemical level.

Einar M. Sigurdsson, PhD, New York University School of Medicine

Dr. Sigurdsson is an Associate Professor of Physiology and Neuroscience, and Psychiatry at New York University School of Medicine. A native of Iceland, he received a master's degree in Pharmacy from the University of Iceland, and a Ph.D. in Pharmacology from Loyola University Chicago Medical Center. He subsequently obtained postdoctoral training at New York University School of Medicine. His current research focuses on pathogenesis, therapy and diagnosis for age-related protein conformational disorders, in particular Alzheimer's and prion diseases, as well as exploratory studies in type-2 diabetes. This endeavor has led to over 50 peer reviewed publications and several patents, issued or pending.

Dr. Sigurdsson and his collaborators pioneered the use of modified Aβ derivatives as potential immunotherapy for Alzheimer's disease. Furthermore, they showed for the first time that active and passive immunization delayed the onset of prion disease in mice. They have now been able to prevent clinical symptoms in a large number of infected mice with a novel oral immunization approach. In addition, they published the first study showing that chelators are a potential therapy for prion disease. On the diagnostic front, Dr. Sigurdsson and colleagues published the initial report on detection of amyloid plaques in living brains by magnetic resonance imaging.

Lately, he has pioneered the approach to harness the immune system to target pathological tau protein, which will be the focus of his presentation. Dr. Sigurdsson is currently supported by the NIH, the Alzheimer's Drug Discovery Foundation and the Alzheimer's Association (Zenith Fellow), and he is a recipient of the Irma T. Hirschl Career Scientist Award.

CLEARANCE OF PATHOLOGICAL TAU CONFORMERS

Einar M. Sigurdsson
New York University School of Medicine

Aggregation of the tau protein is a prominent pathological feature of Alzheimer's disease and related tauopathies but has been an elusive target for therapies. Recently, we have demonstrated in tangle mouse models that immunization with phospho-tau derivatives clears aggregated tau in the brain, and antibody levels against the immunogen correlate inversely with tau pathology. Furthermore, this type of therapy has beneficial effect on their behavioral phenotype, which importantly includes prevention of cognitive impairment in three different tests. The anti-tau antibodies enter the brain and bind to pathological tau within neurons, thereby likely facilitating its lysosomal clearance. As extracellular tau, which is more readily accessible, may have a pathological function and be involved in the spread of tau pathology, its antibody-mediated removal is likely to be helpful as well.

Presently, we are assessing the efficacy of this approach when tau pathology is advanced, clarifying its mechanism of action, and determining its epitope specificity with the ultimate goal to enter clinical trials.

James Moe, PhD, MBA, Oligomerix, Inc.

Dr. Moe received his Ph.D. degree in molecular biology/molecular biophysics from Wesleyan University studying protein-nucleic acid interactions using high field NMR spectroscopy. He did his postdoctoral work at Vanderbilt University in the Center for Molecular Toxicology where he was jointly appointed in the Chemistry Department in the College of Arts and Sciences and the Biochemistry Department in the Medical School determining the solution structure of DNA-carcinogenic adducts. He received his MBA degree with a concentration in entrepreneurial studies from Boston University. His research is currently focused on understanding the molecular basis of protein-protein interactions applicable to neurodegenerative diseases more specifically developing novel drug discovery and biomarker approaches targeting tau oligomers for Alzheimer's disease. He has extensive experience in the biotech/biopharmaceutical industries having worked at various scientific and managerial roles at Gene-Trak/Amoco Technology Ventures/Vysis, bioMerieux, and Mosaic Technologies. Prior to founding OLIGOMERIX he was Director of Product Development at Pyrosequencing and Q-RNA; Inc.

NOVEL APPROACHES FOR TARGETING TAU OLIGOMERES

James Moe
Oligomerix, Inc.

A causative role for tau protein in neurodegenerative diseases is supported by linkage of mutations in the *MAPT* gene to frontotemporal dementia and sporadic tauopathies. These mutations may confer a propensity for aggregation and/or influence the alternative splicing of the primary transcript to usually favor relative overexpression of tau isoforms with four microtubule binding repeats (4R tau) compared to tau isoforms with three repeats (3R tau). There are reports that 4R tau is also elevated in AD, but how this may contribute to pathology is not fully understood. Although tau is predominantly an intracellular protein, facilitating the assembly and stability of microtubules in the axon, increasing reports indicate that extracellular tau may play a role in neurotoxicity and the contiguous spread of tau pathology observed in disease. Reports from work with animal models and AD specimens indicate that the soluble, oligomeric, pre-filamentous aggregates of tau are more toxic than the neurofibrillary tangles that are hallmarks of AD. Here, work will be presented that helps characterize tau oligomers that may model how the relative overexpression of 4R isoforms can contribute to tau oligomer formation. Preliminary work on compound screening targeting tau oligomers will be shown. Additional work will be presented on characterizing extracellular tau in AD and its role in memory impairment in LTP studies using hippocampal brain slices.

IV. ALTERNATIVE STRATEGIES: NEW TARGETS FOR AD THERAPY - Chair: Diana Shineman, PhD, ADDF

PDE9: A New Target for Alzheimer's Disease – Rebecca M. Evans, MD, MSc, Pfizer

Screening for Small Molecule Agonists of Phosphatidylinositol 4-kinase - Tae Wan Kim, PhD, Columbia University Medical Center

Peptidomimetics for Elimination of Cofilin Pathology in Alzheimer's Disease - James R. Bamburg, PhD, Colorado State University

Use of mGluR5 Inhibitors to Modulate Aβ Production, Accumulation And Signaling In Mouse Models Of AD - James S. Malter, MD, University of Wisconsin at Madison

Expedient and Versatile Methods for the Production of Investigational Drugs for SPECT and PET Imaging of AD - Graham Jones, PhD, Northeastern University

Novel Approach to Enhance Cognition through the Dopamine D1 Receptor System by Inhibition of PDE1B- Lawrence P. Wennogle, PhD, Intra-Cellular Therapies, Inc.

Rebecca M. Evans, MD, MSc, Pfizer

Rebecca Evans, MD, MSc is a neurologist and Associate Director of Clinical Neuroscience at Pfizer Global Research and Development. In her current position at Pfizer, she in involved in developing and managing studies in Alzheimer's Disease and stroke. She obtained her MD from the University of Iowa, completed neurology residency training at the University of Minnesota, and completed fellowships in EMG and neuromuscular disease at the University of Kansan, and dementia at Indiana University. Prior to moving to the pharmaceutical industry, she was on the faculty at Indiana University and was an investigator in clinical trials for AD, and engaged in epidemiology and genetics research in AD.

PDE9: A NEW TARGET FOR ALZHEIMER'S DISEASE

Tae-Wan Kim, PhD, Columbia University Medical Center

Dr. Tae-Wan Kim is currently Associate Professor in the Taub Institute for Research on Alzheimer's Disease and the Aging Brain at Columbia University Medical Center (New York, NY). He also holds appointments in the University's Department of Pathology and Cell Biology. Dr. Kim received his B.S. in Biotechnology at Yonsei University (Seoul, Korea), and his Ph.D. in Neurobiology from Rutgers University (Piscataway, NJ) in 1994, while working in the laboratory of the late Dr. Ira B. Black. In 1994, he undertook a postdoctoral fellowship in the laboratory of Dr. Rudolph E. Tanzi at the Massachusetts General Hospital and Harvard Medical School. He was subsequently appointed Instructor and later Assistant Professor of Neurology at Harvard Medical School.

Dr. Kim has received a number of awards, including the Ruth Salta Junior Investigator Achievement Award from the American Health Assistance Foundation (2004), the New Scholar Award in Aging from the Ellison Medical Foundation (2002); and the Partners Investigator Nesson Award from the Partners HealthCare System, Inc. (1998).

Dr. Kim's lab currently focuses on using chemical and functional genetic approaches to understand the biogenesis and synaptic action of β-amyloid peptide and neuronal dysfunction in Alzheimer's disease.

SMALL MOLECULE AGONISTS OF PHOSPHATIDYLINOSITOL 4-KINASE AS POTENTIAL THERAPEUTIC AGENTS IN ALZHEIMER'S DISEASE

Tae-Wan Kim
Columbia University Medical Center

The amyloid β-peptide (Aβ), which originates from the proteolytic cleavage of amyloid precursor protein (APP), plays a central role in the pathogenesis of Alzheimer's disease (AD). Accordingly, targeting various aspects of Aβ metabolism is one of the most promising therapeutic approaches in AD. We and others have previously reported that modulating phosphatidylinositol-4,5-bisphosphate (PI(4,5)P2), a key phospholipid regulating cell signaling and membrane dynamics, inversely modulates Aβ generation. Moreover, Aβ oligomers, the Aβ species known to trigger synaptic dysfunction, caused a profound decrease in the levels of PI(4,5)P2. Thus, modulation of PI(4,5)P2 levels in the neuronal membrane may be involved with both Aβ biogenesis and the synaptic action of Aβ. Phosphatidylinositol 4-kinase type IIα (PI4KIIα) is a lipid kinase that mediates the rate-limiting step in PI(4,5)P2 synthesis. Our preliminary studies revealed that increasing the activity or levels of PI4KIIα led to the reduced secretion of Aβ, in addition to suppression of PI(4,5)P2 depletion triggered by Aβ oligomers. Furthermore, we have identified a natural compound that enhances the activity of PI4KIIα and subsequently confers dual inhibitory effects on both Aβ biogenesis and Aβ-induced synaptic deficits. These results suggest that targeting small molecule-mediated activation of PI4KIIα could serve as a potential new therapeutic strategy in AD.

James R. Bamburg, PhD, Colorado State University

Dr. James Bamburg is Professor of Biochemistry and Molecular Biology and Director of the Molecular, Cellular and Integrative Neuroscience Program at Colorado State University, Fort Collins, CO.

Dr. Bamburg discovered the ADF/cofilin family of proteins while on sabbatical leave at the Laboratory of Molecular Biology, Cambridge, UK in 1979. He has studied the biochemical activity and biological function and regulation of these proteins ever since. These proteins bind actin and form intracellular bundles (rods) in neurons under stress. Rods may be at the heart of synaptic loss leading to cognitive dysfunction in Alzheimer's disease.

PEPTIDOMIMETICS FOR THE ELIMINATION OF COFILIN PATHOLOGY IN ALZHEIMER'S DISEASE

A. E. Shaw[1], B. W. Bernstein[1], R. C. Davis[1], C. Goldsbury[2], M. T. Maloney[1,3], I. T. Marsden[1], L. S. Minamide[1], C. W. Pak[1], I.T. Whiteman[2], J.R. Bamburg[1]
[1]Colorado State University; [2]University of Sydney; [3]Stanford University School of Medicine

Brains from human Alzheimer's disease (AD) patients contain tandem arrays of cofilin immunostaining that appear identical to cofilin-actin rods, which can be induced to form in axons and dendrites of rat hippocampal neurons exposed to a variety of degenerative stimuli. Rods form following neuronal exposure to excitotoxic glutamate, ATP-depleting medium, peroxide, $A\beta_{1\text{-}42}$ oligomers or during anoxia. Rods block intraneurite transport which subsequently leads to distal synaptic loss, connoting their role in mediating the memory and learning deficits of AD. Cofilin-actin rods are necessary for and co-localize with phosphorylated isoforms of tau that occur in the classic "striated neuropil threads" of AD, suggesting rods mediate tau reorganization that may lead to its assembly into paired helical filaments. Together these data suggest that cofilin-actin rods play a major role in the development of AD pathology. To test this hypothesis directly we need either to develop reagents that prevent rod formation but do not inhibit cofilin function, or to identify mutants of cofilin that are functional but do not incorporate into rods. Through analysis of site-directed mutants of cofilin, we have identified surface residue alterations that prevent cofilin incorporation into rods. We are currently testing synthetic peptides of the cofilin sequences encompassing these regions. Peptide activity against rod formation is measured by their microinjection into HeLa cells stably expressing cofilin-GFP and then ATP-depleted. The successful peptide will be able to prevent or reduce the formation of rods without deleterious effects to cell function.

James S. Malter, MD, University of Wisconsin

James S. Malter MD, is a Professor of Pathology and Laboratory Medicine in the University of Wisconsin School of Medicine and Public Health and Associate Director for Biological Sciences in the Waisman Center for Developmental Disabilities, UW-Madison Graduate School. After receiving his AB from Dartmouth College and MD from Washington University, St. Louis, MO., Dr. Malter completed a Clinical Pathology residency and post-doctoral fellowship at the University of Pennsylvania. After a brief stint at Tulane University, Dr. Malter moved to UW-Madison in 1991.

The Malter laboratory currently studies post-transcriptional gene regulation in neurons and immune cells.

USE OF MGLUR5 INHIBITORS TO MODULATE Aβ PRODUCTION, ACCUMULATION AND SIGNALING IN MOUSE MODELS OF AD

C. Westmark, P. R. Westmark, J.S. Malter
University of Wisconsin

Metabotropic glutamate receptors (mGluR) are widely expressed in predominantly post-synaptic, dendritic locations throughout the mammalian hippocampus and cortex. MGluR5 activation induces the selective translation of multiple dendritic mRNAs including amyloid precursor protein (APP) mRNA, a process regulated by the Fragile X Mental Retardation Protein (FMRP). Under resting conditions, FMRP directly interacts with APP mRNA and suppresses its translation. The FMRP-APP mRNA interaction is temporarily lost after mGluR5 signaling, resulting in a burst of dendritic APP synthesis. These data suggested that APP and its conversion to Aβ could be reduced by mGluR5 antagonists. We now show that both *in vivo* and *in vitro*, mGluR5 antagonists rapidly reduce APP production and its cleavage to Aβ. Further we show that both audiogenic and chemically induced seizures are significantly reduced in AD model mice treated acutely with anti-Aβ or mGluR5 antagonists. In aggregate these data suggest that dendritic APP and Aβ production are regulated by mGluR5. The results also suggest that once produced, Aβ may interact with and trigger constitutive mGluR5 signaling, possibly leading to neuronal pathology.

Graham Jones, PhD, Northeastern University

Graham Jones is Professor and Chair of the Department of Chemistry and Chemical Biology. Trained as an organic chemist (in the laboratories of 1990 Nobelist E.J. Corey) his research focuses on the development of new methodology for the chemical synthesis of medicinal candidates and image contrast agents. This includes antitumor antibiotics, antiviral agents and more recently, CNS agents for Huntingtons' disease, Alzheimers disease and Parkinson's disease.

In 2008, Jones established a partnership with the Northeastern Center for Translational Neuroimaging involving synthesis of new probes for SPECT and PET imaging of CNS disorders. His program has generated over 100 publications in the fields of organic and medicinal chemistry, and he has been the recipient of numerous research awards including the DSc in 2006 for contributions to organic and medicinal chemistry. In addition to his role in the department, Jones also serves as Associate Director of The Barnett Institute of Chemical and Biological Analysis where he has been instrumental in developing new research and education programs for the analysis of biomolecules.

EXPEDIENT AND VERSATILE METHODS FOR THE PRODUCTION OF INVESTIGATIONAL DRUGS FOR SPECT AND PET IMAGING OF AD

Graham Jones
Northeastern University

PET and SPECT have becoming significant imaging modalities for the analysis of CNS disorders, providing the potential to track metabolic pathways which can complement the anatomical images provided by magnetic resonance methods. The need for rapid introduction of short half-life radionuclides for use in SPECT and PET imaging presents an ideal application for microwave mediated organic synthesis. Microwave chemical reactors have now evolved to the degree that desktop chemical syntheses can be performed with considerable precision, the microwave method of thermolysis having a substantial accelerating effect on chemical reactions and typically minimizing formation of unwanted byproducts. Using commercially available systems we have developed a number of versatile and proprietary methods for the introduction of ^{18}F, ^{123}I, ^{125}I and other labels to drug candidates for subsequent CNS imaging. The benefits of the Northeastern methods include speed (~5 min reaction time) and clean up – giving rise to extremely pure compounds following simple cartridge filtration. The methods can be applied to introduce the radiolabel either on an alkyl chain or directly on an aromatic (or heteroaromatic) ring. The scope of the process is noteworthy, and we are currently demonstrating applications in the synthesis of FDA approved drugs which possesses fluorine or iodine atoms so that biodistribution studies can be conducted. These include the anti-psychotic agents haloperidol and risperidone and also a series of investigational drugs including the nAChR ligand 5IA-85380, and the nicotine receptor agonist [a4β2] nifrolidine, which are of importance in AD research.

Lawrence P. Wennogle, PhD, Intra-Cellular Therapies

Dr. Wennogle received his Ph.D. in Biochemistry from the University of Colorado, Boulder working under Drs. Howard Berg and Marvin Caruthers where he studied the structure of red blood cell membranes. He then 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 for Torpedo mamorata. For the past 29 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 CNS 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 for schizophrenia in phase 2 clinical trials. Dr. Wennogle is a Fellow of the New York Academy of Sciences (NYAS) and has co-authored over 45 scientific publications. He is a member of the NYAS, the American Association for the Advancement of Science, and the Society for Neurosciences. He has adjunct appointments at Columbia University in the Department of Pharmacology and at University of Medicine and Dentistry, New Jersey in the Graduate School of Biomedical Sciences. His current focus is the development of novel therapeutics for cognitive dysfunction.

NOVEL APPROACH TO ENHANCE COGNITION THROUGH THE DOPAMINE D1 RECEPTOR SYSTEM BY INHIBITION OF PDE1B

Lawrence P. Wennogle
Intra-Cellular Therapies

Hypo-function of the dopamine D1 receptor (D1R) system in the pre-frontal cortex is well established as a deficit that leads to cognitive dysfunction. This mechanism has been extensively studied in connection with schizophrenia, but is broadly implicated to other disorders of cognition. No medicines currently available address this core symptom of cognitive dysfunction. Indeed, most antipsychotic agents only worsen cognition. While direct-acting D1 dopamine receptor agonists have been developed for the treatment of cognitive dysfunction, they have not proven effective in part due to poor bioavailability. In a novel approach to enhance dopamine D1 receptor function, we have developed a series of potent and selective phosphodiesterase 1 (PDE1) inhibitors with good oral bioavailability and pharmacokinetic properties. PDE1 is enriched in the brain and highly abundant in neurons expressing dopamine D1 receptors. D1 receptors signal via stimulation of adenylate cyclase and production of cyclic-AMP. Importantly, prevention of the breakdown of cyclic-AMP by inhibition of PDE1B will result in an "on demand" potentiation of the D1R system, without perturbing dopamine receptor dynamics. PDE1 inhibitors also may enhance NMDA channel activity via modulation of a signal transduction cascade downstream of D1 receptor activation. An advanced development candidate PDE1B inhibitor has been evaluated in a number of animal models of cognition. Our development candidate is a potent (sub-nanomolar), competitive inhibitor of PDE1 with over 1000-fold selectivity for the PDE1 family over other classes of PDE enzymes. After oral administration, the agent enhances cognitive performance in rodents, as judged in the novel object recognition paradigm. It increases wakefulness, but does not disrupt pre-pulse inhibition, alter startle magnitude, influence habituation to startle response, or cause psychomotor stimulation. This candidate has no significant off-target effects, when screened against a panel of 70 unrelated receptors and enzymes. As a novel approach to treat cognitive dysfunction, this mechanism offers unique advantages over direct-acting receptor agonists. The most advanced candidate in this class is currently undergoing pre-clinical development.

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Save the date!

4TH DRUG DISCOVERY FOR NEURODEGENERATION CONFERENCE

HOUSTON, TX • FEBRUARY 1-2, 2010

The purpose of the conference is to advance drug discovery for neurodegenerative disease by educating academic scientists on the processes of translating basic research into novel therapies. The conference will give participants knowledge and relevant resources about this field of scientific investigation; and address the associated barriers and challenges. Speakers and chairs will present lectures and case studies on: **Alzheimer's disease, Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis and Multiple Sclerosis**. Ample time for questions and networking is also integrated into the program.

SESSIONS

I. **Basics of Medicinal Chemistry**

II. **Hits & Leads: Early Phases of Drug Discovery**

III. **Pre-Clinical Proof-of-Concept and Development**

IV. **Issues in Technology Transfer: Interactions and Intellectual Property**

V. **Case Studies**

VI. **Resources and Services for Advancing Drug Discovery**

The objectives of this Alzheimer's Drug Discovery Foundation conference are:

1. To train a cadre of interdisciplinary scientists in the principles of drug discovery for neurodegenerative disease.
2. To provide a platform for scientists to exchange ideas, knowledge and resources about drug discovery for neurodegenerative disease.
3. To stimulate pre-clinical research in the discovery and testing of novel compounds aimed at the prevention and treatment of neurodegenerative disease.
4. To build public-private partnerships that will accelerate drug discovery for neurodegenerative disease.
5. To provide continuing medical education credits.

Alzheimer's Drug Discovery Foundation