The Alzheimer's Drug Discovery Foundation presents:

11TH INTERNATIONAL CONFERENCE ON ALZHEIMER'S DRUG DISCOVERY

September 27-28, 2010

Jersey City, NJ

www.alzdiscovery.org

TABLE OF CONTENTS

WELCOME

On behalf of the Alzheimer's Drug Discovery Foundation (ADDF), I am pleased to welcome you to our *11th International Conference on Alzheimer's Drug Discovery*.

Our annual meeting brings together scientists from around the world engaged in drug discovery for Alzheimer's disease (AD), related dementias and cognitive aging. This year's conference includes a new session on biomarkers as a means to accelerate drug discovery. Other session topics include targeting beta-amyloid, neuroprotection and cognitive enhancement, and anti-tangle strategies for Alzheimer's disease and frontotemporal dementia.

The purpose of the conference is to present and discuss scientific progress on innovative drug discovery programs aimed at treating AD and related dementias. Ample time has been incorporated into the agenda for networking and to facilitate partnerships between academic, biotechnology and pharmaceutical companies.

This meeting is made possible by the generous support of our sponsors. We are deeply grateful for their sponsorship. We would also like to thank our exhibitors and media partners for their contributions. Our sincere appreciation also extends to all of our speakers and chairs for the hard work they do in their quest to find a cure for Alzheimer's disease.

Please visit the poster presentations by our young investigator scholarship winners. We are proud of their efforts and encourage them to continue pursuing their work in the field.

As this is an annual meeting, we ask that you use the enclosed survey to provide us with feedback to help us plan an even better conference in 2011.

Welcome, once again, to the *11th International Conference on Alzheimer's Drug Discovery*!

Best Regards,

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

ABOUT THE ALZHEIMER'S DRUG DISCOVERY FOUNDATION

MISSION

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

The 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.

The 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 $40M for more than 300 research programs and conferences worldwide.

OUR CONFERENCES

The ADDF 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 ADDF also plans smaller "catalyst conferences" that center around a relevant topic in the field of neurodegeneration.

PROGRAM

Sunday, September 26	
5:00–7:00 pm	**On-Site Pre-Registration**
Monday, September 27	
8:00 – 8:30am	**Registration & Continental Breakfast**
8:30 – 8:40	**Welcome & Opening Remarks**
	Howard Fillit, MD, Alzheimer's Drug Discovery Foundation
8:40 – 9:15	**Plenary Lecture: Biomarker Implementation in Alzheimer's Drug Development**
	Holly Soares, PhD, Bristol-Myers Squibb
I. Biomarkers to Accelerate Drug Discovery Chair: Holly Soares, PhD, Bristol-Myers Squibb	
9:15 – 9:20	**Session Overview – Holly Soares, PhD, Bristol-Myers Squibb**
9:20 – 9:40	**Predictive Imaging for the Diagnosis of Dementia**
	Dawn C. Matthews, MS, MBA, Abiant, Inc.
9:40 – 9:50	***Q&A***
9:50 – 10:10	**Metabolics in the Study of Alzheimer's Disease**
	Rima Kaddurah-Daouk, PhD, Duke University Medical Center
10:10 – 10:20	*Q&A*
10:20 – 10:50	**BREAK / VIEW POSTERS**
10:50 – 11:10	**Frontotemporal Lobar Degeneration (FTLD) Biomarker Assays**
	Linda K. Kwong, PhD, University of Pennsylvania School of Medicine
11:10 – 11:20	*Q&A*
11:20 – 11:40	**Application of Immunosignatures to the Assessment of Alzheimer's Disease**
	Stephen A. Johnston, PhD, Arizona State University Foundation
11:40 – 11:50	*Q&A*
11:50 am – 12:10 pm	**Combined CSF Biomarkers and Genotype for Diagnosis of Lewy Body Dementia (LBD)**
	Lawrence S. Honig, MD, PhD, FAAN, Columbia University
12:10 – 12:20	*Q&A*
12:20 – 1:30	**LUNCH / VIEW POSTERS**
II. Targeting Beta-Amyloid Production and Clearance Chair: Sidney Strickland, PhD, The Rockefeller University	
1:30 – 1:35	**Session Overview – Sidney Strickland, PhD, The Rockefeller University**
1:35 – 1:55	**Fibrinogen and B-Amyloid Association Alters Thrombosis and Fibrinolysis: A Possible Contributing Factor to Alzheimer's Disease**
	Sidney Strickland, PhD, The Rockefeller University
1:55 – 2:05	*Q&A*
2:05 – 2:25	**Microvascular Blood Flow Disruptions in the Vicinity of Amyloid Plaques**
	Chris B. Schaffer, PhD, Cornell University
2:25 – 2:35	*Q&A*
2:35 – 2:55	**RAGE Blocker and Alzheimer's Disease**
	Rashid Deane, PhD, University of Rochester
2:55 – 3:05	*Q&A*
3:05 – 3:35	**BREAK / VIEW POSTERS**
3:35 – 3:55	**Screening for Chemical Modifiers of BACE1-Mediated Cleavage of APP**
	Tae-Wan Kim, PhD, Columbia University
3:55 – 4:05	*Q&A*
4:05 – 4:25	**The Therapeutic Potential of ABCA1 and ApoE for Alzheimer's Disease**
	Cheryl L. Wellington, PhD, University of British Columbia
4:25 – 4:35	*Q&A*
4:35 – 4:55	**Is Alzheimer's Disease a Disorder of Mitochondria-associated Membranes?**
	Eric A. Schon, PhD, Columbia University
4:55 – 5:05	*Q&A*
5:05 – 5:10	**Closing Remarks**
	Diana Shineman, PhD, Alzheimer's Drug Discovery Foundation
5:10 – 7:00	**NETWORKING RECEPTION / VIEW POSTERS**

Tuesday, September 28	
8:00 – 8:30 am	**Continental Breakfast**
8:30 – 9:05	**Plenary Lecture: Alzheimer's Disease Modeling with Patient-specific Stem Cells**
	Scott A. Nogle, PhD, The New York Stem Cell Foundation
III. Neuroprotection and Cognitive Enhancement Chair: Roberta Diaz Brinton, PhD, University of Southern California in Los Angeles	
9:05 – 9:10	**Session Overview – Roberta Diaz Brinton, PhD, University of Southern California in Los Angeles**
9:10 – 9:30	**Allopregnanolone as a Neurogenic Factor for Recovery of Neurons in Alzheimer's Disease**
	Roberta Diaz Brinton, PhD, University of Southern California in Los Angeles
9:30 – 9:40	*Q&A*
9:40 – 10:00	**Novel PDE5 Inhibitors as a Therapeutic Tool Against Alzheimer's Disease**
	Ottavio Arancio, MD, PhD, Columbia University
10:00 – 10:10	*Q&A*
10:10 – 10:30	**Development of Klotho Enhancers as Novel Therapeutics for Alzheimer's Disease**
	Carmela R. Abraham, PhD, Boston University School of Medicine
10:30 – 10:40	*Q&A*
10:40 – 11:10	**BREAK / VIEW POSTERS**
11:10 – 11:30	**Small Molecule Blockade of Abeta 42 Oligomer-induced Memory Deficits**
	Susan Catalano, PhD, Cognition Therapeutics Inc.
11:30 – 11:40	*Q&A*
11:40 am– 12:00 pm	**Screening for Inhibitors of STEP**
	Paul J. Lombroso, MD, Yale University
12:00 – 12:10	*Q&A*
12:10 – 12:30	**GABA A α5 Agonist Therapy for Conditions Specific to Neurocognitive Aging**
	Michela Gallagher, PhD, Johns Hopkins University
12:30 – 12:40	*Q&A*
12:40 – 1:45	**LUNCH / VIEW POSTERS**
IV. Anti-Tangles and Frontotemporal Dementia Chair: Michael S. Wolfe, PhD, Harvard University	
1:45 - 1:50	**Session Overview – Michael Wolfe, PhD, Harvard University**
1:50 – 2:10	**Aminothienopyridazine Inhibitors of Tau Aggregation**
	Carlo Ballatore, PhD, University of Pennsylvania School of Medicine
2:10 – 2:20	*Q&A*
2:20 – 2:40	**Targeting Tau Pre-mRNA for Frontotemporal Dementia and Related Disorders**
	Michael S. Wolfe, PhD, Harvard University
2:40 – 2:50	*Q&A*
2:50 – 3:10	**PP2A: A Novel Therapeutic Target for Alzheimer's Disease**
	Jeffry Stock, PhD, Signum Biosciences
3:10 – 3:20	*Q&A*
3:20 – 3:50	**BREAK / VIEW POSTERS**
3:50 – 4:10	**Immunotherapy for Clearing Pathological Tau Protein**
	Einar M. Sigurdsson, PhD, New York University School of Medicine
4:10 – 4:20	*Q&A*
4:20 – 4:40	**Tau Clearance by Macroautophagy**
	Wai Haung Yu, PhD, Columbia University
4:40 – 4:50	*Q&A*
4:50 – 5:00	**Closing Remarks**
	Howard Fillit, MD, Alzheimer's Drug Discovery Foundation

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PharmaVOICE

Alzheimer's Daily News

Save the dates!

FEEDING THE PIPELINE: NOVEL TARGETS FOR ALZHEIMER'S DRUG DISCOVERY

November 3, 2010, Toulouse, France

A one-day meeting focusing on European biotechnology companies conducting early-stage, high risk research for Alzheimer's disease. This is a satellite meeting to be held in conjunction with the *3rd Clinical Trials on Alzheimer's Disease* (CTAD) conference.

6TH INTERNATIONAL PHARMACOECONOMIC CONFERENCE ON ALZHEIMER'S DISEASE

February 3-4, 2011, King's College, London, England

This is the only conference that exclusively addresses issues related to the economic evaluation of drug treatments for Alzheimer's. The conference brings together leading experts and opinion leaders from academia, regulatory bodies and the pharmaceutical industry. The ADDF co-hosts with the Karolinska Institutet, Stockholm.

TARGETING IMPAIRED SYNAPTIC PLASTICITY

May 18, 2011, New York, New York

Optimal functioning of neural networks is key to the complex thought, emotion, and memories that deteriorate in Alzheimer's disease. Understanding these networks and their synaptic connections is crucial to developing new drugs to protect and maintain neuronal function and vitality. This one-day conference will provide an overview on synaptic plasticity and relevant neural networks and outline therapeutic strategies to preserve these vital connections. ADDF co-hosts the meeting with the New York Academy of Sciences.

2010 ADDF YOUNG INVESTIGATOR SCHOLARSHIP RECIPIENTS

Congratulations to the winners of the 2010 **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.

The 2010 Young Investigator Scholars are:

De-ming Chau, *Cornell Medical College*

Paige Cramer, *Case Western Reserve University*

Michael Gertner, *Albert Einstein College of Medicine*

Heather A. Menchen, *University of Kansas*

Angela McKoy, *Princeton University*

Suhail Rasool, *University of California - Irvine*

Michal Richman, *Bar-Ilan University*

Reeteka Sud, *University of Pennsylvania School of Medicine*

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

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.

Holly Soares, PhD, Bristol-Myers Squibb

Holly Soares is currently a Director at Bristol-Myers Squibb (BMS) and heads the Neuroscience Clinical Biomarkers group. Dr. Soares obtained a BS in Neuroscience from Oberlin College and a PhD in Biomedical Science from the University of Connecticut Health Science Center. She completed a post-doctoral fellowship at St. Jude Children's Research Hospital and went on to jointly serve as an Assistant Professor at the Morehouse School of Medicine and as an Investigator at the Center for Behavioral Neuroscience, an Atlanta University based consortium including Morehouse, Emory University, Georgia Tech and Georgia State. Prior to joining BMS, Dr. Soares was a Director of Translational Medicine at Pfizer Inc. where she led the Alzheimer's disease biomarker portfolio and ensured experimental compounds targeted for Alzheimer's disease demonstrated proof-of-mechanism prior to entering late stage development testing. Throughout her career, Dr. Soares has been recognized for excellence in research and is the recipient of the MSM Dean's award and Pfizer's Above and Beyond award. She has been a leader in the AD biomarker field and served as chair on key precompetitive partnerships in Alzheimer's disease including the Alzheimer's Disease Neuroimaging Consortium (ADNI), the fNIH Biomarkers Consortium AD proteomics group and the Coalition Against Major Disease (CAMD) AD biomarker qualification group. In her current position at BMS, Dr. Soares ensures biomarkers are used to increase the success rate in proof-of-concept studies through biomarker demonstration of target engagement, improve successful Phase III studies through biomarker implementation in targeted patient selection and safety monitoring and ensure biomarker tools are available for life-cycle management of marketed compounds.

PLENARY LECTURE:
Biomarker Implementation in Alzheimer's Drug Development

Holly Soares

Bristol-Myers Squibb

Alzheimer's disease is a challenging disease to diagnose and identify during early stages of the disease. Much of modern drug development has focused upon targets thought to intervene during early stage pathology and success is high dependent upon the ability to identify patients during stages of the disease where pathology may not be severely advanced. Biomarkers have revolutionized the ability to identify patients during pre-dementia stages of disease and are critical tools for AD drug development. The current treatise will illustrate how biomarkers are being used to demonstrate target engagement in drug development and as tools to identify patients suitable for AD clinical trials.

I. Biomarkers to Accelerate Drug Discovery
Chair: Holly Soares, PhD, Bristol-Myers Squibb

Predictive Imaging for the Diagnosis of Dementia
Dawn C. Matthews, MS, MBA, Abiant, Inc.

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Application of Immunosignatures to the Assessment of Alzheimer's Disease
Stephen A. Johnston, PhD, Arizona State University Foundation

Combined CSF Biomarkers and Genotype for Diagnosis of Lewy Body Dementia (LBD)
Lawrence S. Honig, MD, PhD, FAAN, Columbia University

Dawn C. Matthews, MS, MBA, Abiant, Inc.

Dawn Matthews is President and CEO of Abiant, Inc., a company specializing in the development and application of highly accurate imaging-based measures of disease and drug response in central nervous system disorders. Ms. Matthews brings 24 years of experience in medical device and biotechnology industries with an emphasis on managing the development and commercialization of advanced technologies to address unmet medical needs. Previously, she served as CEO of MIICRO, Inc., and as Director of Business Development for Motorola BioChip Systems. Prior to that, she was a Co-Founder, Vice President, and Acting Chief Financial Officer of Aksys, Ltd., a company that developed a novel system to enable kidney patients to perform hemodialysis on a near daily basis. Earlier, she held positions including Senior Principal Engineer in the Renal and Clintec Nutrition Divisions at Baxter Healthcare. Ms. Matthews received her BS in Electrical Engineering from the University of Notre Dame, her MS in Electrical Engineering from the University of Michigan, and her MBA from Northwestern University.

Predictive Imaging for the Diagnosis of Dementia

Dawn C. Matthews

Abiant, Inc.

Imaging biomarkers provide a highly sensitive, objective means to address the need for reliable measures of disease, disease progression, and drug response in dementias of aging. Positron Emission Tomography (PET) imaging of glucose metabolism provides a measure of regional brain function that precedes and correlates with clinical progression, while amyloid imaging gives a specific measure of plaque pathology that is now known to manifest in very early stages of the disease. Complementing these is Magnetic Resonance Imaging (MRI), which can measure subtle changes in volume in the hippocampus and other relevant brain structures.

Imaging biomarkers can be used to qualify study populations, provide information regarding drug impact upon pathology and brain function, and reduce outcome measure variance, yielding information that can be used for cost-effective decision making. In the clinical setting, these biomarkers can facilitate the distinction between Alzheimer's Disease and other dementias, and enable the early detection of disease, allowing optimal treatment choices when intervention can be most effective. Critical to the use of imaging biomarkers are quality control methods and analysis approaches that enable reliable results and that can distill complexity to interpretable metrics, in combination with high quality reference data sets. These have been made possible through the development of specialized tools and through the collection of comprehensive data sets by the Alzheimer's Disease Neuroimaging Initiative, similar efforts in other countries, and data collected by other imaging sites.

A goal of this session is to share information and specific examples regarding the qualitative and quantitative imaging measures that are achievable within the clinical setting and within drug development trials, in support of decision-making and the successful treatment of patients faced with dementia.

Rima Kaddurah-Daouk, PhD, Duke University Medical Center

Dr. Kaddurah-Daouk trained in biochemistry at the American University of Beirut with post graduate training in molecular biology and genetics at Johns Hopkins (where she worked with Nobel Laureate Hamilton Smith) and the Massachusetts General Hospital followed by appointment in the Biology department at the Massachusetts Institute of Technology. She is currently an Associate Professor at the Duke University Medical Center and head of the newly established Pharmacometabolomics Center. Dr. Kaddurah-Daouk has been a seminal force in the development and evolution of the metabolomics field. She co-founded the Metabolomics Society, served as its founding president and for over four years organized national and international meetings and workshops on metabolomics. She also co-founded a leading biotechnology company devoted to metabolomics applications. Dr. Kaddurah-Daouk has extensive experience in assembling teams of researchers to work collaboratively on large scientific projects and has led scientific programs from an early stage of discovery through clinical trials. She established and leads the Metabolomics Research Network with funding from National Institute of General Medical Sciences (NIGMS) (R24 grant and RC2 stimulus funding) with the goal of integration of metabolomics and clinical pharmacology in an effort to personalize treatment. Additionally she has built a comprehensive metabolomics program at Duke University Medical Center for mapping biochemical underpinnings in neuropsychiatric diseases. Her work with the creatine kinase system earlier in her career resulted in the identification of neuroprotective properties of creatine which is currently being tested in phase III clinical trials in 50 centers for Parkinson's and Huntington's diseases.

Metabolics in the Study of Alzheimer's Disease

Rima Kaddurah-Daouk[1]*, Steve Rozen[1,2], Wayne Matson[3], Xianlin Han[4], Christine M. Hulette[5,6], James R. Burke[5] , P. Murali Doraiswamy[1], Kathleen A. Welsh-Bohmer[1,5]

[1]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, [2]Duke-NUS Graduate Medical School, Singapore, [3]Department of Systems Biochemistry, Bedford VA Medical Center, Bedford, Mass, [4]Department of Medicine, Washington University, St. Louis, [5]Bryan Alzheimer Disease Research Center, Duke University, [6]Department of Pathology, Duke University

Biomarkers that are specific and sensitive to Alzheimer's disease (AD) would facilitate early diagnosis, disease progression monitoring and drug development. Prior neurochemical and metabolic (e.g., neurotransmitter studies and PET scans) studies have focused on studying a small number of metabolites, and while important findings were derived, no robust biomarkers for AD have been identified. Metabolomics, the global science of biochemistry, provides powerful tools to map perturbations in the metabolic network and enables simultaneous quantification of a large number of metabolites to identify metabolic signatures as biomarkers for disease. We used a couple of metabolomics platforms to map biochemical signatures in plasma and CSF samples from AD patients. Targeted electrochemistry based metabolomics approach where liquid chromatography is followed by coulometric array detection (LCECA) enables quantification of over thirty metabolites within key neurotransmitter pathways dopamine and serotonin and pathways involved in oxidative stress. Samples from post-mortem ventricular cerebrospinal fluid (CSF) (15 AD and 15 non-demented subjects with autopsy confirmed diagnoses) profiled using the LCECA platform and using regression models, correlations, Wilcoxon rank-sum tests and t-tests revealed major alterations in norepinephrine pathway and related pathways. Lipidomics analysis of 50 plasma samples from AD patients and control subjects highlighted changes in specific sphingomyelins and ceramide species. These data support further investigation of these profiles in larger samples of clinical AD for utility as biomarkers.

Linda K. Kwong, PhD, University of Pennsylvania School of Medicine

Linda K. Kwong is Senior Research Investigator in the Center for Neurodegenerative Disease Research at the University of Pennsylvania. After receiving her BS in Biology from the University of California, Irvine (1971) and her PhD in Biochemistry from University of Wyoming (1976), she did her post-doctoral training in the Department of Pediatrics at Stanford University studying efficacy of a pyrimidne analog as antiproliferative agent for cancer therapy. She remained at Stanford University studying developmental gastroenterology. Over the years, her research interests included aging and lipid dysfunction in diabetes mellitus. She was a member of the team at the Center for Neurodegenerative Disease Research (CNDR) that discovered TDP-43 as a major disease protein in the inclusions in both FTLD-U and ALS. Her current research focus is the functions and dysfunctions of TDP-43.

Frontotemporal Lobar Degeneration (FTLD) Biomarker Assays

Linda K. Kwong

University of Pennsylvania School of Medicine

Frontotemporal dementia (FTLD) is a group of clinically, genetically and pathologically heterogeneous disorders that results from the selective progressive degeneration of the frontal and the temporal lobes of the brain. Clinically, patients may present with behavioral and/or language dysfunction. Additionally, they may display movement abnormalities such as parkinsonism or motor neuron disease. FTLD can be divided into two broad neuropathological groups, those with tau-positive inclusions in the affected areas (FTLD-tau, e.g. Pick's disease, corticobasal degeneration (CBD), progressive supranuclear palsy (PSP)) and those with tau-negative, but ubiquitin-positive inclusions (FTLD-U). The *TARDP*-encoded protein TDP-43 was found to be the major disease protein in ~80% of the FTLD-U cases (FTLD-TDP) as well as in the majority of sporadic amyotrophic lateral sclerosis (ALS). Cerebrospinal fluid (CSF) tau levels did not distinguish between FTLD-tau and FTLD-TDP making it difficult for differential diagnosis of these diseases. Thus, additional biomarkers are needed to characterize the two groups. Using multi-analyte profiling analysis, we identified 2 putative CSF biomarkers that were elevated in FTLD-TDP when compared to FTLD-tau: agouti-related peptide and interleukin 17. We have also developed a sensitive sandwich ELISA to measure TDP-43 levels in biofluids. Preliminary data showed varying higher plasma TDP-43 levels in clinical FTLD and AD patients when compared to PD and normal controls. Further study using samples from autopsy confirmed cases will determine if plasma TDP-43 level has diagnostic utility in antemortem diagnosis FTLD-TDP. In conclusion, the newly discovered putative biomarkers along with the established CSF Aβ42, total tau, and p-tau biomarkers would aid in diagnosis, prognosis and treatments of FTLD.

Stephen A. Johnston, PhD, Arizona State University Foundation

Dr. Johnston directs the Center for Innovations in Medicine (CIM) at the new Biodesign Institute. CIM is unique in its focus on inventing disruptive technologies in biomedicine. Current efforts are focused on developing a universal, prophylactic cancer vaccine and an in-house biosignature diagnostic device. His center also has a project aimed at creating a system for fast and systematic vaccine development. Dr. Johnston largely focuses on invention. He was inventor or co-inventor or innovator of pathogen derived resistance, mitochondrial transformation, TEV protease system and others. Relative to vaccines, he was co-inventor of the gene gun, gene immunization, expression library immunization, linear expression elements, synbodies and immunosignaturing. He has been an advisor on biosecurity issues for many years.

Application of Immunosignatures to the Assessment of Alzheimer's Disease

Lucas Restrepo, Phillip Stafford, D. Mitch Magee and Stephen A. Johnston

Center for Innovations in Medicine, Biodesign Institute, School of Life Sciences, Arizona State University

Accurate assessment of Alzheimer's disease (AD), both pre-symptomatically and at different disease stages, will become increasingly important with the expanding elderly population. There are a number of indications that the immune system is engaged in AD. We are exploring the ability of an antibody-profiling technology we have developed, immunosignatures, to characterize AD. Immunosignaturing is a simple, inexpensive, array-based technique that uses random peptide, spotted slides to profile the antibody diversity in a person.

We have applied the immunosignaturing technique to the sera of transgenic mice with cerebral amyloidosis (TG) and elderly individuals with or without AD.

The TG mice exhibited a distinct immunosignature compared to non-transgenic littermates. Further, we show that dementia patients, including autopsy-confirmed AD subjects, have distinguishable profiles compared to age-matched non-demented people. Using antibodies to different forms of Aβ peptide and blocking protocols, we demonstrate that most of this signature is not due to the subject's antibodies raised against Aβ. Interestingly, the AD signature consists of reactivities both higher and lower than non-AD controls. Based on these results we are continuing to explore immunosignaturing as an AD diagnostic.

Lawrence S. Honig, MD, PhD, FAAN, Columbia University

Dr. Honig is a neurologist and neuroscientist at Columbia University, with subspecialty expertise in Alzheimer's and other neurodegenerative diseases. He has an AB degree from Cornell University (NY), a PhD from the University of California, Berkeley (CA), and an MD from the University of Miami (FL). He is a Fellow of the American Academy of Neurology, and a member of the American Neurological Association and the Society for Neuroscience. He is ABMS Board-Certified in Neurology, and has UCNS subspecialty certifications in both Behavioral Neurology/Neuropsychiatry and Geriatric Neurology. Dr. Honig performs basic, translational, and clinical research involving Alzheimer's disease, Lewy Body Dementia, and other cognitive disorders. He is an expert clinician who leads the inpatient neurobehavioral consultation service at New York Presbyterian Hospital, and performs outpatient neurobehavioral consultations and patient care. His research focus is on biomarkers in neurodegenerative disease including studies of gene expression, and genetic and epigenetic (telomere) markers in Lewy Body Disease, frontotemporal dementias, vascular cognitive impairment, Alzheimer's disease and aging. He is the director of the Clinical Core of the NIA/NIH-funded Alzheimer's Disease Research Center (ADRC) at Columbia University. He is the principal site investigator in a number of ongoing clinical drug trials and neuroimaging trials in Alzheimer's and other neurodegenerative disorders.

Combined CSF Biomarkers and Genotype for Diagnosis of Lewy Body Dementia (LBD)

Lawrence S. Honig

Columbia University

Lewy Body Dementia (LBD) is the second most common neurodegenerative dementia, after Alzheimer's Disease (AD). There is substantial overlap between the symptoms of AD and LBD. Accurate clinical diagnosis of LBD has proven difficult. The prognosis and course of these disorders differ, and different treatment strategies will likely emerge. Lewy bodies in the brainstem are the pathological hallmark of Parkinson's Disease, but their more widespread distribution in the brain is common at autopsy. Lewy bodies are found in a spectrum of conditions in addition to clinical Lewy Body Dementia, including Parkinson's Disease without dementia, Parkinson's Disease with dementia, and AD. About one third of persons suffering from clinical AD have some pathological findings of concomitant Lewy body involvement. For AD, biomarkers including cerebrospinal fluid (CSF) proteins (beta-amyloid, tau, and phosphotau), genotype (apoE), and molecular brain imaging have shown increasing utility. Data on LBD will be reviewed here, regarding value of biomarkers in distinguishing LBD from AD. CSF may show a pattern of reduced beta-amyloid but relatively normal tau and phosphotau levels, and possibly increased alpha-synuclein in LBD. Genotypes of ApoE are less informative in LBD, but genetic variants in glucocerebrosidase (GBA) gene are associated with Lewy body disorders. Brain imaging nuclear medicine studies of dopamine transporters may also assist in diagnosis of LBD. Combined use of these CSF, genotype, and molecular imaging markers may provide for improvements in LBD diagnosis.

II. Targeting Beta-Amyloid Production and Clearance
Chair: Sidney Strickland, PhD, The Rockefeller University

Fibrinogen and B-Amyloid Association Alters Thrombosis and Fibrinolysis: A Possible Contributing Factor to Alzheimer's Disease
Sidney Strickland, PhD, The Rockefeller University

Microvascular Blood Flow Disruptions in the Vicinity of Amyloid Plaques
Chris B. Schaffer, PhD, Cornell University

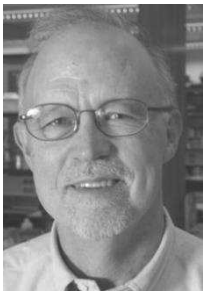
RAGE Blocker and Alzheimer's Disease
Rashid Deane, PhD, University of Rochester

Screening for Chemical Modifiers of BACE1-Mediated Cleavage of APP
Tae-Wan Kim, PhD, Columbia University

The Therapeutic Potential of ABCA1 and ApoE for Alzheimer's Disease
Cheryl L. Wellington, PhD, University of British Columbia

Is Alzheimer's Disease a Disorder of Mitochondria-associated Membranes?
Eric A. Schon, PhD, Columbia University

Sidney Strickland, PhD, The 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. He 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 and B-Amyloid Association Alters Thrombosis and Fibrinolysis: A Possible Contributing Factor to Alzheimer's Disease

Marta Cortes-Canteli*, Justin Paul*, Erin H. Norris, Robert Bronstein, Hyung Jin Ahn, Daria Zamolodchikov, and Sidney Strickland

The Rockefeller University

Alzheimer's disease (AD) is a neurodegenerative disorder in which vascular pathology plays an important role. Since the β-amyloid peptide (Aβ) is a critical factor in this disease, we examined its relationship to fibrin clot formation in AD. *In vitro* and *in vivo* experiments showed that fibrin clots formed in the presence of Aβ are structurally abnormal and resistant to degradation. Fibrin(ogen) was observed in blood vessels positive for amyloid in mouse and human AD samples, and intravital brain imaging of clot formation and dissolution revealed abnormal thrombosis and fibrinolysis in AD mice. Moreover, depletion of fibrinogen lessened cerebral amyloid angiopathy pathology and reduced cognitive impairment in AD mice. These experiments suggest that one important contribution of Aβ to AD is via its effects on fibrin clots, implicating fibrin(ogen) as a potential critical factor in this disease.

**These authors contributed equally*

Chris B. Schaffer, PhD, Cornell University

Chris Schaffer received his undergraduate degree from the University of Florida in 1995 and his PhD from Harvard University, working with Eric Mazur, in 2001. Both of his degrees are in Physics. As a post-doc at UCSD, Dr. Schaffer worked with David Kleinfeld in the Physics and Neuroscience departments. He is currently an Assistant Professor at Cornell University in the Department of Biomedical Engineering. His research centers on the development and use of advanced optical tools for in-vivo manipulation and quantitative imaging of biological structures. These new tools are used to study the biological mechanisms that underlie a variety of neurological diseases, with a focus on small stoke, Alzheimer's disease, spinal cord injury, epilepsy, and cancer.

Microvascular Blood Flow Disruptions in the Vicinity of Amyloid Plaques

Nozomi Nishimura[1], Jeff Beverley[1], Gabriel Otte[1], Joan Zhou[1], Elizabeth Slack[1], Costantino Iadecola[2], and Chris B. Schaffer[1]

[1]Cornell University, [2]Weill Cornell Medical College

Alzheimer's disease is characterized by a loss of cognitive function that is caused by the dysfunction and death of neurons in the brain. This cell injury is likely due, in part, to toxic effects of aggregates of a small peptide, amyloid-beta, which eventually accumulates into dense plaques scattered throughout the brain. Recent work has shown local damage to neurons as well as locally increased inflammation near these plaques, suggesting that the plaques create a toxic microenvironment that could affect many functions. In addition, recent clinical research in humans and experimental work in animals suggesting that blood flow to the brain is impaired in Alzheimer's disease, suggesting vascular dysfunction could be one result of this toxic microenvironment. We used in vivo two-photon excited fluorescence microscopy to examine the blood flow in microvessels in the brain of transgenic mouse models of Alzheimer's disease. In this imaging method, we fluorescently label the blood vessels by intravenous injection of a dye, allowing us to image the location and structure of the blood vessels in three dimensions in the brain. This labeling strategy also enables us to determine whether individual brain microvessesl are flowing or not, by taking advantage of the fact that the injected dye labels only the blood plasma, so the non-fluorescent red blood cells produce dark patches, which can be seen as moving or stalled. Additionally, we can fluorescently label the amyloid plaques that are the pathological hallmark of Alzheimer's disease and determine whether stalled vessels are more frequent near these plaques. In ~9 month old wild-type mice, we found the fraction of capillaries stalled in the cortex to be 0.3%, while in same-aged Alzheimer's mice this fraction rises to 1.8% (2475 capillaries across four wild-type and 2843 capillaries across six Alzheimer's mice, $p < 0.001$). Because vessels immediately downstream from a stalled capillary are slowed, this six-fold increase in capillary stalls represents a significant decrease in the overall blood flow to the brain. Our current work focuses on determining the stability of these capillary stalls and determining whether they are caused by activated leukocytes adhering to regions of inflamed endothelium.

Rashid Deane, PhD, University of Rochester

Dr. Rashid Deane was born in South America, educated, resided and worked in England until he joined the team of Dr. Berislav Zlokovic in 2002, to work on Alzheimer's disease (AD). His interest in the CNS vascular barriers (blood-brain barrier (BBB) and blood-CSF barrier (choroid plexus)) in health and disease started during his undergraduate studies at the University of London, under the guidance of the late Dr. W. F. Widdas. Dr. Deane received his PhD training at St. Thomas's Hospital in London, supervised by Dr. M.B. Segal, an expert on the choroid plexus. He then received a brief training on cerebrospinal fluid (CSF) flow and its dynamics in developing rats in the laboratory of Dr. Hazel Jones at the University of Hull. Concepts of BBB dysfunction were developed during his postdoctoral fellowship at the King's College, in the laboratory of Prof. M. B. Bradbury, a BBB expert, where they elucidated the mechanism of lead transport across the BBB and into CSF. In 2002, he was fortunate to join Dr. Berislav Zlokovic at the University of Rochester, one of the leading neurovascular experts who was conducting pioneering work on the vascular concept of AD and neurodegeneration. Here, he pursued his investigation of the role of RAGE and low-density lipoprotein related-receptor 1 (LRP1) in the transport of Aβ across the BBB, and on their control of Aβ levels in brain parenchyma. This led to the investigation on RAGE blockers as a potential therapy for AD, and for other RAGE related diseases.

RAGE Blocker and Alzheimer's Disease

Rashid Deane[1*], Itender Singh[1*], Abhay Sagare[1], Robert Bell[1], Nathan T. Ross[2], Barbara Larue[1], Rachal Love[1], Sheldon Perry[1], Nicole Paquette[1], Richard J Deane[1], Thiyagarajan Meenakshisundaram[1], Troy Zarcone[3], Alan Friedman[4], Benjamin L. Miller[2], Berislav V. Zlokovic[1]

[1]Center of Neurodegenerative and Vascular Brain Disorder, [2]Depts. of Biochemistry and Biophysics, and Dermatology and [3,4]Dept. of Environmental Medicine, University of Rochester

Amyloid-β peptide (Aβ) interaction with receptor for advanced glycation end products (RAGE) on cells of the neurovascular unit regulates cerebral blood flow (CBF), neuroinflammation and brain Aβ levels. In brains of AD patients and in mouse models of AD, RAGE (receptor for advanced glycation end products) expression is increased on cells of the neurovascular unit, particularly in an Aβ rich environment. Thus, compounds which block Aβ/RAGE interaction at the BBB and/or cells within the brain may have multiple actions, such as reducing neuroinflammation, improving CBF regulation and cognitive decline and reducing brain Aβ levels, which should have beneficial therapeutic effects in AD. Therefore, we screened a library of 5,000 small compounds to identify possible molecules which may block Aβ/RAGE interaction on RAGE overexpressed on Chinese hamster ovary (CHO) cells (RAGE-CHO cells). A tertiary amide (FPS2), was identified which competitively antagonizes Aβ/RAGE interaction on RAGE-CHO cells. In APPsw$^{+/-}$ mice with and without significant amyloid-β deposits, it reduced Aβ40 transport from the circulation into brain, across the blood-brain barrier (BBB), and improved functional CBF and cognitive deficits, and reduced neuroinflammation and Aβ pathology. FPS-ZM1, a designed analog of FPS2, with greater BBB permeability and potency than FPS2, reduced levels of proinflammatory cytokines and Aβ production by blocking NF-κB activation and NF-κB mediated β-secretase (BACE) activity in mainly microglia and neurons, respectively. FPS-ZM1 was more effective than FPS2 in improving functional CBF and cognition in APPsw$^{+/-}$ mice with prominent amyloid-β deposits. By extension, FPS-ZM1 could be used to target RAGE mediated neuroinflammation, and improve functional CBF and cognitive deficits in Alzheimer's disease.

Tae-Wan Kim, PhD, Columbia University

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 BS in Biotechnology at Yonsei University (Seoul, Korea), and his PhD 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.

Screening for Chemical Modifiers of BACE1-Mediated Cleavage of APP

Tae-Wan Kim

Columbia University

The amyloid β-peptide (Aβ) is produced by sequential proteolytic cleavage of β-amyloid precursor protein (APP) by a set of membrane-bound proteases termed β-secretase (BACE1) and γ-secretase. The level of Aβ in the brain is critically associated with both pathological and behavioral/clinical phenotypes of AD. Thus, CNS penetrable small molecules that can reduce Aβ in an effective and safe manner remains one of the most promising approaches for the prevention or treatment of AD. While a number of direct small molecule inhibitors of β- or γ-secretase have been developed, many of them have suffered side effects, including target-associated toxicity. In the present study, we conducted reverse chemical genetic studies to identify small molecule inhibitors of BACE1-mediated cleavage of APP with a goal to ultimately identify a putative protein target of the small molecule. In order to identify inhibitors that act via a novel mechanism, we developed a cell-based assay in intact neuronal cells, based on antibody-mediated specific capture of the BACE1-derived secreted APP ectodomain (sAPPβ) fused to a secreted alkaline phosphatase (SEAP) reporter. By screening small molecule libraries using this cell system, we identified small molecules that can inhibit BACE1-mediated cleavage of APP without directly interfering with BACE1 activity. One such compound was subjected to medicinal chemistry to improve the bioactivity and the resulting compound (termed C2) reduces Aβ levels in cultured primary neurons as well as a mouse model of AD. We are currently investigating a putative cellular target for this compound. Identification of a small molecule modifier of the Aβ generation pathway and elucidating its mechanism of action may serve as the foundation for development of new therapeutic agents that could modify pathological phenotype associated with AD, such as elevated brain levels of Aβ.

Cheryl L. Wellington, PhD, University of British Columbia

Dr. Wellington obtained her PhD in Microbiology at the University of British Columbia (UBC) in 1991 and did postdoctoral training at Harvard Medical School, University of Chicago, and UBC. She joined the Department of Pathology and Laboratory Medicine at the UBC in 2000 and was promoted to Associate Professor in 2006. Dr. Wellington's research investigates lipid and lipoprotein metabolism in the brain and how this relates to neurological disorders. Lipoprotein metabolism in the central nervous system (CNS) is based entirely upon lipoproteins that resemble plasma high-density lipoproteins (HDL; the "good cholesterol") in density, size and composition. The major difference between brain and plasma HDL is that apolipoprotein E (apoE) is the predominant protein constituent of brain HDL compared to apoA-I in plasma HDL. ApoE is the major cholesterol carrier in the brain and the most established genetic risk factor for Alzheimer's disease (AD) in the general population. Exactly how apoE affects the pathogenesis of AD has been a leading question in the AD field since the discovery of apoE's genetic association with AD in 1993. Dr. Wellington's research program has shown the amount of lipids that apoE carries directly affects the clearance of Aβ peptides, which are the toxic species that accumulate in the brains of AD patients. Specifically, her group demonstrated that genetic loss of the cholesterol transporter ABCA1 in the murine brain impairs apoE lipidation and promotes amyloid deposition. Conversely, selective overexpression of ABCA1 increases apoE lipidation in the CNS and is sufficient to completely prevent the formation of amyloid plaques in mouse models of AD. These discoveries raise the possibility that augmenting the ABCA1-apoE pathway may be a promising therapeutic strategy for AD. Her present research projects are focused on developing therapeutic approaches for AD based on the ABCA1-apoE pathway.

The Therapeutic Potential of ABCA1 and ApoE for Alzheimer's Disease

Cheryl L. Wellington

University of British Columbia

Apolipoprotein E (apoE) is the major component of brain HDL and the most validated genetic risk factor for Alzheimer's Disease (AD). The cholesterol transporter ABCA1 moves lipids onto apoE as the rate-limiting step in brain lipoprotein biosynthesis. In AD mice, ABCA1 deficiency exacerbates amyloidogenesis, whereas selective overexpression of ABCA1 ameliorates amyloid burden. Liver X Receptor (LXR) agonists such as GW3965, which stimulate ABCA1 and apoE expression, reduce Aβ levels and rescue cognitive deficits in AD mice. However, current LXR agonists are not yet safe to use in humans due to the unavoidable side effect of inducing hepatic steatosis and hypertriglyceridemia. To safely develop the therapeutic potential of the ABCA1-apoE pathway for AD, we have performed a high throughput screen for compounds that enhance apoE secretion from astrocytoma cells. Of 3,580 known compounds screened, a known LXR agonist and a class of compounds with known neuroprotective activity were identified. Of 25,989 additional chemical structures screened, two compounds with confirmed concentration-dependent activity were identified. Further development of these compounds into AD therapeutics will be discussed.

Eric A. Schon, PhD, Columbia University

Eric A. Schon, PhD, is the Lewis P. Rowland Professor of Neurology (in Genetics and Development) at Columbia University. His laboratory studies the molecular genetics of neurological and neuromuscular diseases, with particular focus on mitochondrial disorders. The research has two principal goals: (1) to use the tools of molecular biology in order to gain insight into the etiology, pathogenesis, and treatment of these devastating diseases, and (2) to build on this knowledge in order to ask more fundamental biological questions relating to nuclear-mitochondrial communication, mitochondrial biogenesis, mtDNA plasticity, and structure-function relationships of respiratory chain enzymes. Most recently, the laboratory has become interested in understanding the structural and functional relationships between mitochondria and the endoplasmic reticulum in the pathogensis of Alzheimer disease.

Is Alzheimer's Disease a Disorder of Mitochondria-associated Membranes?

Eric A. Schon, Estela Area-Gomez

Columbia University

We have discovered that mitochondria-associated membranes (MAM) - a specialized subcompartment of the endoplasmic reticulum (ER) involved in lipid metabolism and calcium homeostasis that physically connects ER to mitochondria - is the predominant subcellular location for Presenilins-1 and -2, and for γ-secretase activity. We hypothesize that presenilins play a role in maintaining MAM function, and that not only hyperphosphorylated tau and altered Ab levels, but also many other features of AD (e.g. altered cholesterol and phospholipid metabolism, aberrant calcium homeostasis, and abnormal mitochondrial dynamics), result from compromised MAM function. The localization of presenilins and γ-secretase in MAM may help reconcile disparate ideas regarding the pathogenesis of AD, under a unifying hypothesis that could explain many features of both sporadic and familial AD, thereby taking AD research in a new and fruitful direction.

CLOSING REMARKS
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.

Scott A. Nogle, PhD, The New York Stem Cell Foundation

Scott A. Noggle, PhD, is Director of Laboratory and Senior Research Fellow at The New York Stem Cell Foundation Laboratory and Adjunct Associate Research Scientist in Pediatrics and Molecular Genetics at Columbia University. He was a postdoctoral fellow in the lab of Ali H. Brivanlou at The Rockefeller University where he previously managed the Stem Cell Derivation Core facility and studied the signaling pathways that maintain pluripotency and control neural induction. He received his PhD from the Medical College of Georgia.

PLENARY LECTURE:
Alzheimer's Disease Modeling with Patient-specific Stem Cells

Scott A. Nogle

The New York Stem Cell Foundation

Many diseases, including degenerative disorders like Alzheimer's disease, result from the destruction of specific cell types. In order to develop effective treatments for these disorders, it is essential that we understand why these cells are lost and how to prevent their loss. The development of cell reprogramming technologies to generate patient-specific stem cell lines offers an unprecedented opportunity to develop these models and to probe molecular and cellular aspects of the disease. Once reprogrammed stem cell lines have been created from a particular individual, their self-renewal and differentiation capacity allow the production of an endless supply of the particular human cell types necessary to study functional ramifications of an individual's genotype. We are applying these new advances in cell reprogramming to generate human models of Alzheimer's disease which we hope will open new avenues for drug discovery.

III. Neuroprotection and Cognitive Enhancement
Chair: Roberta Diaz Brinton, PhD, University of Southern California in Los Angeles

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Allopregnanolone as a Neurogenic Factor for Recovery of Neurons in Alzheimer's Disease
Roberta Diaz Brinton, PhD, University of Southern California in Los Angeles

Novel PDE5 Inhibitors as a Therapeutic Toll Against Alzheimer's Disease
Ottavio Arancio, MD, PhD, Columbia University

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

Small Molecule Blockade of Abeta 42 Oligomer-induced Memory Deficits
Susan Catalano, PhD, Cognition Therapeutics Inc.

Screening for Inhibitors of STEP
Paul J. Lombroso, MD, Yale University

GABA A α5 Agonist Therapy for Conditions Specific to Neurocognitive Aging
Michela Gallagher, PhD, Johns Hopkins University

Roberta Diaz Brinton, PhD, University of Southern California in Los Angeles

Dr. Roberta Diaz Brinton is Professor of Pharmacology and Pharmaceutical Sciences and Biomedical Engineering at the University of Southern California. Professor Brinton leads a successful scientific research program to discover neural mechanisms of memory and neuron survival (pharmweb.usc.edu/brinton-lab/). Importantly, her research team is translating their discoveries into therapeutics for prevention of and recovery from neurodegenerative diseases especially Alzheimer's. Her research has focused on developing optimal safe hormone therapies for prevention of Alzheimer's disease in postmenopausal women who are the major victims of the disease. Dr. Brinton's research is also investigating neural mechanisms of learning and developing therapeutics to treat learning disabilities and autism. Dr. Brinton has published over 100 scientific reports and serves on scientific review boards for the National Institutes of Health and the Institute for the Study of Aging. She serves on the scientific advisory board of the Alzheimer's Drug Development Foundation and the Diabetes Insipidus Foundation. Dr. Brinton is also the co-founder of a biotechnology company and holds several patents for therapeutics. Dr. Brinton has served for 16 years as Director of the USC Science, Technology and Research Program (pharmweb.usc.edu/USCSTAR/). She was recently named by US News & World Report as a "Best Mind" and was awarded Outstanding Woman of the 24th California State Senatorial District. Dr. Brinton earned her PhD in Psychobiology and Neuropharmacology from the University of Arizona as a National Institutes of Health Predoctoral fellow. She continued her postdoctoral research in Neuroendocrinology at The Rockefeller University as a National Institutes of Health postdoctoral fellow and joined the USC faculty in 1988.

Allopregnanolone as a Neurogenic Factor for Recovery of Neurons in Alzheimer's Disease

Roberta Diaz Brinton

University of Southern California in Los Angeles

Ottavio Arancio, MD, PhD, Columbia University

Dr. Ottavio Arancio received his PhD and MD from the University of Pisa, Italy. From 1981 to 1986 he took residency training in Neurology at the University of Verona. Dr. Arancio has held Faculty appointments at Columbia University, NYU School of Medicine and at SUNY HSCB. In 2004, he became Faculty member of the Department of Pathology and Taub Institute for Research on Alzheimer's Disease and the Aging Brain at Columbia University. His honors include the "G. Moruzzi Fellowship" (Georgetown University), the "Anna Villa Rusconi Foundation Prize" (Italy), and the "INSERM Poste vert Fellowship" (France), Fidia Fellowship (Italy); Speaker's Fund for Biomedical Research Award; Investigator Initiated Research Award and the Zenith Award (Alzheimer Association); AHAF Centennial Award, and the 2008 Margaret Cahn Research Award. Dr. Arancio is a cellular neurobiologist who has contributed to the characterization of the mechanisms of learning in both normal conditions and during neurodegenerative diseases. During the last ten years he has pioneered the field of mechanisms of synaptic dysfunction in Alzheimer's disease. Dr. Arancio's laboratory has focused primarily on events triggered by amyloid protein. These studies, which have suggested new links between synaptic dysfunction and amyloid protein, are of a general relevance to the field of Alzheimer's disease both for understanding the etiopathogenesis of the disease and for developing therapies aiming to improve the cognitive symptoms.

Novel PDE5 Inhibitors as a Therapeutic Toll Against Alzheimer's Disease

Ottavio Arancio

Columbia University

One of the important targets for developing a causal therapy for Alzheimer's disease (AD) is represented by synapses. The nitric oxide signaling pathway is thought to play an important role in the synapse during plasticity and memory. Published data from my laboratory have demonstrated the involvement of the pathway in amyloid-beta-induced synaptic dysfunction (Puzzo et al, J. Neurosci. 25:6887– 6897, 2005). Most importantly, sildenafil, an inhibitor the cGMP-degrading enzyme phosphodiesterase V (PDE5), produces an immediate and long lasting amelioration of synaptic and memory abnormalities in an amyloid-depositing mouse model, the APP/PS1 animal (Puzzo et al, J. Neurosci. 29:8075– 8086, 2009). None of the existing PDE5 inhibitors has been developed to counteract diseases of the CNS and at the same time possesses the selectivity required for chronic administration to an elderly population with comorbid conditions such as AD patients. Thus, in collaboration with the laboratory of Dr. Landry at Columbia University, we have launched a project aiming at the identification of molecules that, by enhancing cGMP levels, re-establish normal synaptic plasticity and cognition in the APP/PS1 mouse model. A compound, termed YF012403, has shown high potency (IC_{50} = 0.27 nM) and excellent selectivity for PDE5 over all of the other PDE isoforms. We have also found that this compound crosses the blood-brain barrier after p.o. administration with a T_{max}=0.5 hr and a C_{max}=385 ng/g at a dosage of 50 mg/kg, and is safe up to 2 g/kg (p.o.) in acute toxicity test. Most importantly, YF012403 was biologically active in tests of synaptic and cognitive function following elevation of amyloid-beta. We are now refining this molecule.On the completion of these studies we will identify a new drug for the treatment of cognitive loss in AD.

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

Dr. Abraham was first introduced to Alzheimer's disease research in 1980. Since then, she has participated in the purification of the proteins involved in plaque and tangle formation, identified alpha1-antichymotrypsin as a amyloid binding protein and an important inflammation-related factor, searched for the physiologic function of APP, searched for the beta-secretase, and identified an Abeta-degrading enzyme. Dr. Abraham obtained her PhD in Neuroscience from Harvard University and joined Boston University School of Medicine in 1989 where she became a Professor in 1999. Her laboratory studies the molecular mechanisms leading to normal brain aging and the pathological processes that culminate in Alzheimer's disease.

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

Carmela R. Abraham

Boston University School of Medicine

To successfully design AD therapeutics, changes occurring early in the disease process must be targeted for therapeutic development. Increased oxidative stress is observed in brain, prior to the onset of AD. Work from our lab found the anti-aging protein Klotho to be down regulated in the brains of aged non-human primates at a time when cognitive impairment develops in these animals. Mice overexpressing Klotho have extended lifespan and enhanced resistance to oxidative stress. Conversely, the absence of Klotho protein results in mice that develop and mature normally only to rapidly decline and die from a plethora of phenotypes resembling human aging, including osteoporosis, arthrosclerosis and cognitive decline. Klotho is generated in the kidney and in brain by neurons and the choroid plexus. However, most studies have focused on Klotho function in kidney. The unique brain phenotype of Klotho knockout animals suggests that Klotho may have brain specific functions and be affected by aging processes. Klotho knockout brains are deficient in Purkinje cells, have aberrant axonal transport, show upregulation of apoptotic proteins, reduced expression of synaptic proteins, and mice are deficient in long-term memory retention. To determine whether enhancing Klotho levels is neuroprotective we developed a high throughput-screening platform utilizing the Klotho promoter driving luciferase expression and screened a library of 150,000 small molecules to identify compounds that increase Klotho expression. Of 401 hits, 10 compounds were evaluated for their effects on Klotho protein expression and function. All 10 compounds increase endogenous Klotho protein expression in opossum kidney cells. The 4 most robust compounds were chosen for further protein studies and functional testing. Compounds also increased endogenous Klotho levels in Z310 rat choroid plexus cells. Further functional analysis is underway to determine the mechanism of Klotho promoter activation. We will now begin chemical modifications to optimize the molecules for testing in animals. Klotho's role in antioxidant defense and calcium homeostasis may indicate that its downregulation is involved in the earliest events leading to neurodegenerative disorders making it an interesting target for novel therapeutic development.

Susan Catalano, PhD, Cognition Therapeutics Inc.

Dr. Catalano has over ten years of experience as a cell biologist in the drug discovery industry in the fields of neuroscience and oncology. Dr. Catalano received her PhD from U.C. Irvine and postdoctoral training at U.C. Berkeley and Caltech in the field of neurobiology. While a scientist at Roche Palo Alto, she held leadership positions in the Neurophysiology and Neuroimaging groups and led an exploratory program against protein targets involved in anxiety, depression and schizophrenia. Following this, Dr. Catalano joined Rigel Pharmaceuticals, Inc. and pioneered the use of high content phenotypic screening technology to discover an Aurora kinase inhibitor currently in Phase II clinical trials. Dr. Catalano founded a successful consulting practice, Drug Discovery Imaging. She then served as Director of Discovery Biology for Acumen Pharmaceuticals, Inc., where she led the effort to develop some of the first small molecule screens to target toxic Abeta oligomers in the industry. Dr. Catalano founded Cognition Therapeutics Inc. to discover drugs to treat or prevent Alzheimer's disease, and established Cognition's laboratory operations in Pittsburgh in February 2008. The company is currently advancing its lead small molecule series in efficacy studies.

Small Molecule Blockade of Abeta 42 Oligomer-induced Memory Deficits

Susan Catalano

Cognition Therapeutics Inc.

Abeta 1-42 oligomers accumulate in the brains of patients with Mild Cognitive Impairment (MCI) and begin to disrupt the balance of associative and dissociative synaptic plasticity processes that underlie memory formation (Knobloch and Mansury '08, Selkoe '08). Synaptic binding of oligomers to neuronal surface proteins inhibits synaptic plasticity phenomenon such as LTP, affects membrane trafficking, induces reversible spine loss in hippocampal neurons, and impairs spatial memory (Shrestha et al., '06, Hsieh et al., '06, Calabrese et al., '07, Shankar et al., '07, LaCor et al.,'07, Lesne et al., '06, Cleary et al., '05). These changes ultimately result in anterograde amnesia in the early stages of Alzheimer's disease (Marcello et al., '08, Viola et al., '08). Small molecules that rapidly block the negative effects of Abeta oligomers on the molecular mechanisms of synaptic plasticity underlying memory have the potential to be disease-modifying Alzheimer's therapeutics. We have discovered several structurally distinct compound series that eliminate the effects of Abeta oligomers on membrane trafficking in primary neurons. These molecules appear to act via partial antagonism of Abeta oligomer binding to the surface of the neuron and/or prevention of oligomer structure, are plasma stable (t1/2 = 3hrs) and are capable of reaching high concentrations in the brain (brain/plasm ratio of 8 at 3 hours, 57 times the behaviorally efficacious concentration). Representative members of these compound series were tested in the fear conditioning behavioral task for their ability to preserve normal associative memory. Compounds were injected bilaterally via intrahippocampal cannula (2 pmol) one hour prior to the injection of Abeta 1-42 oligomers (200nM total Abeta) in wild-type C57Bl/6mice. After an additional 20 minutes, animals received a mild electric foot shock. Animals were tested for context-dependent learning 24 hours later. Animals receiving Abeta oligomer injections exhibited significant memory deficits as measured by decreased freezing behavior vs. vehicle (13 +/- 2% vs. 27 +/- 1% respectively). Compounds administered prior to Abeta oligomer completely blocked the effects of Abeta oligomers on memory (CT0109 =30 +/- 2%, CT0093 = 25 +/- 1%), and had no effect on memory when administered without Abeta oligomers (CT0109 =28 +/- 1%, CT0093 = 31 +/- 1%). Administration of these compounds does not induce motor deficits or abnormal behavior. These compounds represent promising Alzheimer's therapeutics.

Paul J. Lombroso, MD, Yale University

Dr. Lombroso discovered the STEP family of tyrosine phosphatases approximately 20 years ago and has been studying its role in learning and memory. As will be discussed today, STEP has been implicated in several neuropsychiatric disorders, including Alzheimers disease, schizophrenia, and fragile X syndrome. Dr. Lombroso received his training at Albert Einstein College of Medicine, Harvard University and Rockefeller University before coming to Yale University. He is the Director of the Laboratory of Molecular Neurobiology and House Jameson and Elizabeth Mear Professor in the Child Study Center, Departments of Psychiatry and Neurobiology.

Screening for Inhibitors of STEP

Paul J. Lombroso

Yale University

STriatal-Enriched protein tyrosine Phosphatase (STEP) is elevated in several neuropsychiatric diseases including Alzheimer's disease, schizophrenia and fragile X syndrome. STEP dephosphorylates several key signaling proteins and inactivates them. The increase in STEP levels leads to internalization of AMPA and NMDA receptors, which is thought to contribute to the cognitive deficits in these devastating illnesses. Results will be presented of how genetic and pharmacological reduction in STEP activity reverses cognitive deficits in an animal model of Alzheimer's disease.

Michela Gallagher, PhD, Johns Hopkins University

Dr. Michela Gallagher received her BA from Colgate University in 1969 and PhD 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.

GABA A α5 Agonist Therapy for Conditions Specific to Neurocognitive Aging

Michela Gallagher

Johns Hopkins University

Recent research on neurocognitive aging has focused on increased neural activity that drives dysfunction underlying memory impairment in the hippocampal network. Excess neural activity in the CA3 region of the hippocampus occurs in aged rats with memory impairment when such neurons are unable to encode new information in the manner usually observed in young rats. Reports of increased hippocampal activation in age-related memory impairment and amnestic mild cognitive impairment (aMCI) have now been similarly localized to the CA3 subregion of hippocampus in humans using fMRI. Several methods have been used in animal studies to show that decreasing this excess activity improves memory performance in aged rats and a clinical study is now underway to test the use of low dose antiepileptic therapy in aMCI. An ideal target for therapy in a condition of such excess activity could be the use of agonists with selectivity for GABA A α5 subunit containing receptors. These receptors have exceedingly limited expression in the mammalian brain and are known to mediate tonic inhibition in hippocampal pyramidal neurons where they are strongly expressed. This proposed use of GABA A a5 agonists to treat memory impairment may seem somewhat paradoxical because GABA A α5 inverse agonists have been developed as potential cognitive enhancers. Nonetheless, using a series of agonists in tests of cognition in aged rats, memory performance was improved and this effect was blocked by selective α5 inverse agonist administration. Thus GABA A α5 agonists offer a novel approach to therapy specific for a condition of overactivity associated with memory loss in aging. Because this hippocampal overactivity is a condition in man that predicts further cognitive decline and conversion to Alzheimer's disease, GABA A α5 agonists may also have disease modifying potential.

IV. Anti-Tangles and Frontotemporal Dementia
Chair: Michael S. Wolfe, PhD, Harvard University

Aminothienopyridazine Inhibitors of Tau Aggregation
Carlo Ballatore, PhD, University of Pennsylvania School of Medicine

Targeting Tau Pre-mRNA for Frontotemporal Dementia and Related Disorders
Michael S. Wolfe, PhD, Harvard University

PP2A: A Novel Therapeutic Target for Alzheimer's Disease
Jeffry Stock, PhD, Signum Biosciences

Immunotherapy for Clearing Pathological Tau Protein
Einar Sigurdsson, PhD, New York University School of Medicine

Tau Clearance by Macroautophagy
Wai Haung Yu, PhD, Columbia University

Carlo Ballatore, PhD, University of Pennsylvania School of Medicine

Dr. Carlo Ballatore is a Research Assistant Professor at the University of Pennsylvania School of Medicine, Center for Neurodegenerative Disease Research. His research focuses on drug discovery in the area of Alzheimer's disease and related tauopathies. Dr. Ballatore graduated in Chemistry and Pharmaceutical Technologies at the University of Rome "La Sapienza", Rome, Italy. He obtained a PhD in Medicinal Chemistry at the University of Wales, Cardiff, UK.

Aminothienopyridazine Inhibitors of Tau Aggregation

Carlo Ballatore

University of Pennsylvania School of Medicine

Alzheimer's disease (AD) and related neurodegenerative tauopathies are characterized by the presence of insoluble proteinaceous deposits (*e.g.*, neurofibrillary tangles, or NFTs) comprised of hyperphosphorylated tau proteins. Although the exact mechanism of tau-mediated neurodegeneration is not fully defined, there is evidence to suggest that tau misfolding and aggregation can have neuropathological consequences via toxic gains and/or losses of function. As a result, agents capable of preventing tau misfolding and sequestration into insoluble aggregates hold promise for the prevention and/or treatment of these serious diseases. Here we report the identification of a novel class of tau aggregation inhibitors, the aminothienopyridazines, and describe a series of new analogues that are both effective inhibitors of tau fibrillization and display significant brain-to-plasma exposure ratios after administration to mice.

Michael S. Wolfe, PhD, Harvard University

Michael S. Wolfe received his BS in chemistry in 1984 from the Philadelphia College of Pharmacy and Science and earned his PhD 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.

Targeting Tau Pre-mRNA for Frontotemporal Dementia and Related Disorders

Michael S. Wolfe

Harvard University

The microtubule-associated protein tau is strongly implicated in the pathogenesis of frontotemporal dementia (FTD) and related disorders. However, its role in the pathogenic process is not understood, and tau is underdeveloped as a therapeutic target. Major clues are over 30 mutations in the tau gene that cause FTD (*1*). Many of these mutations are silent and alter the splicing of the tau pre-mRNA, leading to increased inclusion of exon 10 and thereby shifting the balance between tau proteins that contain 3 or 4 microtubule binding repeat domains (3R and 4R tau, respectively). We have validated a postulated stem-loop at the junction between exon 10 and intron 10 as a *bona fide* structure that regulates 3R versus 4R tau formation in cells (*2*). We have also carried out a high-throughput screen and identified the anti-cancer drug mitoxantrone (MTX) as a small molecule that binds to and stabilizes this stem-loop structure (*3*). Tau pre-mRNA stem-loop stabilizers have therapeutic potential, as their effect is opposite that of FTD-causing mutations. More recently, we have determined the structure of MTX bound to the tau stem-loop by NMR (*4*) and validated this bound structure through analogue design, synthesis and evaluation (*5*). We have also been pursuing a novel antisense strategy for targeting the tau stem-loop structure, preliminary findings for which will be presented.

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3. Donahue, C. P., Ni, J., Rozners, E., Glicksman, M. A., and Wolfe, M. S. (2007) Identification of tau stem loop RNA stabilizers, *J Biomol Screen 12*, 789-799.
4. Zheng, S., Chen, Y., Donahue, C. P., Wolfe, M. S., and Varani, G. (2009) Structural basis for stabilization of the tau pre-mRNA splicing regulatory element by novantrone (mitoxantrone), *Chem Biol 16*, 557-566.
5. Liu, Y., Peacey, E., Dickson, J., Donahue, C. P., Zheng, S., Varani, G., and Wolfe, M. S. (2009) Mitoxantrone analogues as ligands for a stem-loop structure of tau pre-mRNA, *J Med Chem 52*, 6523-6526.

Jeffry B. Stock, PhD, Signum Biosciences

Jeffry B. Stock is Professor of Molecular Biology and Chemistry at Princeton University. His principal research interest is concerned with the biochemistry and biophysics of signal transduction with an emphasis on reversible post-translational modifications such as phosphorylation and carboxyl methylation. He holds a PhD in Biochemistry from Johns Hopkins University where he performed seminal studies on chemiosmotic mechanisms that underlie the active transport of sugars in bacteria. Dr. Stock went on to do postdoctoral research at the University of California, Berkeley where began research on bacterial chemotaxis. In 1982 he moved to Princeton where he elucidated the his-asp phosphorelay signal transduction mechanism that regulates chemotaxis responses and gene expression in bacteria. In parallel studies with a variety of different eukaryotic systems, he has elucidated roles for reversible methylation in the regulation of RAS-related and heterotrimeric G-protein signalling as well as in the regulation of phosphoprotein phosphatase PP2a activity. Dr. Stock founded Signum Biosciences, a biotechnology start up dedicated to the development of novel pharmaceuticals for the treatment of signal transduction imbalances associated with inflammation and neurodegenerative disease. He is a member of the Center Review Committee for the National Institute of Drug Abuse, serves on several editorial boards, and is a fellow of the American Association for the Advancement of Science and the American Academy of Microbiology.

Phosphoprotein Phosphatase 2A (PP2A): A Novel Pharmaceutical Target for the Treatment of Alzheimer's Disease

Jeffry B. Stock

Signum Biosciences

Signaling imbalances due to aberrant protein phosphorylation play a critical role in the pathogenesis and progress of Alzheimers's disease (AD). The development of therapeutics to correct these imbalances have focused almost entirely on inhibiting kinase activities towards key targets such as the microtubule associated protein, tau. Activation of phosphatases such as protein phosphatase 2A (PP2A) to correct signaling imbalances is a promising alternative approach. The PP2A holoenzyme comprising A, Bα & C subunits accounts for over 50% of total phosphatase activity in the brain. Carboxyl methylation of the catalytic C-subunit of PP2A enhances the formation and stability of ABαC. Methylation is catalyzed by a highly specific PP2A methyl transferase (PPMT), and demethylation is catalyzed by a specific methyl esterase (PME). Considerable evidence suggests that low levels of PP2A activity associated with decreased levels of PP2A methylation play a key role in tau hyperphosphorylation and neuronal cell death [Vafai, S.B. & Stock, J.B. (2002) FEBS Lett., 518, 1-4.] Building on these observations, we reasoned that an agent that inhibited PP2A demethylation might be useful for the prevention and treatment of AD. To establish proof of principle for this approach, we developed an in vitro biochemical assay for PP2A demethylation, and identified an appropriate pharmaceutical lead, Sig1012. Sig1012 is an easily synthesized small molecule (<500 mw) that is orally-bioavailable, readily crosses the blood brain barrier; and, in preliminary studies with mice, shows an excellent safety profile. Mice maintained for 3 or more weeks on a diet supplemented with Sig1012 show dramatically reduced levels of tau hyperphosphorylation. These and related findings strongly support the notion that pharmaceutical agents that enhance PP2A holoenzyme stability by inhibiting C-subunit demethylation provide a promising therapeutic approach for the treatment of AD.

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 PhD 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.

Immunotherapy for Clearing Pathological Tau Protein

Einar M. Sigurdsson

New York University School of Medicine

Harnessing the immune system to target pathological tau protein has recently become attractive as a potential therapy for tauopathies such as frontotemporal dementia (FTD) and Alzheimer's disease (AD). We previously showed that active immunization targeting a disease-related phospho-tau epitope reduces cerebral tau aggregates in mice and slows progression of the FTD tau mutation-related behavioral phenotype. Furthermore, we have observed that this approach prevents cognitive decline in an AD tangle model, and that the therapeutic benefit is at least in part mediated by anti-tau antibodies. In our studies, these antibodies enter the brain and bind to pathological tau within neurons, thereby likely facilitating its lysosomal clearance. Recent reports that extracellular tau is important for the anatomical spread of tau pathology strengthen as well the feasibility of clearing disease-related tau protein, as this pool should be more accessible for removal.

The promise of tau immunotherapy has now been confirmed by other groups. We are currently pursuing various active and passive immunization approaches targeting several regions within the pathological tau protein at different stages of the disease in several mouse models. The overall objective of these studies is to enter clinical trials in the near future.

Wai Haung Yu, PhD, Columbia University

W. Haung (Ho) Yu is an Assistant Professor at the Taub Institute for Research on Alzheimer's disease and the Aging Brain in the Department of Pathology and Cell Biology at Columbia University. He received his PhD in Pharmacology from the University of Toronto and subsequently completed a postdoctoral fellowship at Nathan Kline Institute and New York University and was funded by the Canadian Institutes of Health Research (CIHR). His research interests have included the biochemical and pathological analysis of Alzheimer's and Parkinson's diseases (AD and PD), focusing on cellular and neuropathological effects of protein aggregation (tau, synuclein, Ab) and the autophagic-lysosomal systems. These studies have led to over 25 peer-reviewed publications and review chapters, including work published in high-profile journals that include Cell, Journal of Cell Biology, Journal of Neuroscience, Neuron and American Journal of Pathology. Currently, Dr. Yu's lab is focusing on validating drug targets for the treatment of proteinopathies, including inducing autophagy, a mechanism for the bulk clearance of protein aggregates and dysfunctional mitochondria. He is also studying the mechanisms of action and dysfunction of the autophagic-lysosomal system in genetic mouse models of proteinopathies associated with AD and PD.

Tau Clearance via Macroautophagy

Wai Haung Yu

Columbia University

Tau aggregation is a hallmark of many neurodegenerative disorders, including Alzheimer's disease (AD), fronto-temporal dementia (FTD) and polysupranuclear palsy (PSP). The accumulation of tau manifests in various neurological deficits, including cognitive and motor dysfunction, as well as impairment of cellular transport. While significant research advances have been made in identifying the biophysical events associated with the protein misfolding and the kinases/phosophatases that alter tau function, there is renewed emphasis in identifying biochemical processes involved in preventing or reversing tauopathy. Macroautophagy is one such mechanism and is the principle cellular mechanism for the clearance of large protein aggregates, such as aggregated tau. It is an essential process in the maintenance of healthy neurons. Recent work has also shown that the use of rapamycin can increase the longevity of laboratory mice. In this study, we report that the autophagic pathway can be utilized to reduce the levels of tau aggregates in animal models and induction of autophagy was successful in reversing tau accumulation in three organotypic models of tauopathy and reduce motor defects observe in the JNPL3 mouse over a 2 month period. Cumulatively, this study supports the use of autophagic induction agents for the clearance of tau aggregates and potential prevention of tauopathy-related dementia.

This research was funded by the ADDF-FTD and CurePSP foundations.

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