The Alzheimer's Drug Discovery Foundation presents:

13th INTERNATIONAL CONFERENCE ON ALZHEIMER'S DRUG DISCOVERY

September 10-11, 2012
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 *13th International Conference on Alzheimer's Drug Discovery*.

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

We are deeply grateful to our generous sponsors whose support makes this meeting possible: Eli Lilly & Company, Merck Research Laboratories; Pfizer Inc.; Elan Pharmaceuticals, Inc.; GlaxoSmithKline; Janssen; NeuroPhage Pharmaceuticals, Inc.; Genentech; Satori Pharmaceuticals Inc.; PsychoGenics; Baxter Healthcare Corporation; Abbott Laboratories Inc.; and JSW Life Sciences GmbH. We would also like to thank our exhibitors and media partners for their contribution. Our sincere appreciation also extends to all of our speakers and chairs for the hard work they do to accelerate drug discovery for Alzheimer's disease and related dementias.

Engaging the next generation of research scientists in this field is more important than ever and we are pleased to announce our 2012 Young Investigator Scholarship winners. We encourage you to visit their poster presentations which will be displayed throughout the meetings.

To help us plan an even better conference in 2013, please complete the survey to provide us with feedback and suggestions.

Welcome, once again, to the *13th International Conference on Alzheimer's Drug Discovery*!

Best Regards,

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

ABOUT THE ALZHEIMER'S DRUG DISCOVERY FOUNDATION

CONQUERING ALZHEIMER'S THROUGH DRUG DISCOVERY

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

Founded in 1998 by Co-Chairmen Leonard and Ronald Lauder, the Alzheimer's Drug Discovery Foundation (ADDF) awards grants to leading scientists conducting breakthrough drug discovery and early clinical research.

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

WHAT WE'VE ACCOMPLISHED

- The ADDF has granted more than **$51 million to fund 370 Alzheimer's drug discovery programs and clinical trials** in academic centers and biotechnology companies in **18 countries**.
- Many of the ADDF's grants are structured as loans or investments which provide a return that can be reinvested in new grants. From $12.7 million invested to date in biotechnology company grants, **$2.4 million has come back to the ADDF so far as returns on investment** – and has been committed to new research.

OUR CONFERENCES

The Alzheimer's Drug Discovery Foundation organizes two annual international scientific conferences as part of our ongoing efforts to increase researchers' knowledge about Alzheimer's disease and the drug discovery process. The conferences promote networking to catalyze the exchange of ideas and foster alliances that accelerate the development of new treatments for AD.

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

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

PROGRAM

Sunday, September 9	
5:00–7:00	**On-Site Pre-Registration**
Monday, September 10	
8:00 – 8:30	**Registration & Continental Breakfast**
8:30 – 8:50	**Welcome & Opening Remarks** Howard Fillit, MD, Alzheimer's Drug Discovery Foundation
8:50 – 9:30	**Plenary: Clinical Development of Neuroprotective Peptide, *Davunetide*** Michael Gold, MD, Allon Therapeutics Inc.
I. Neuroprotection: Aβ, Tau, and Mitochondria Function Chair: Diana Shineman, PhD, Alzheimer's Drug Discovery Foundation	
9:30 – 9:35	**Session Overview: Diana Shineman, PhD, Alzheimer's Drug Discovery Foundation**
9:35 – 9:55	**Orally Active Bioavailable Metal Attenuating Compounds for Alzheimer's Disease** Peter F. Kador, PhD, University of Nebraska Medical Center
9:55 – 10:05	*Q&A*
10:05 – 10:25	**Development and Efficacy Evaluation of Novel Immunotherapy for Human Tauopathies** Kun Ping Lu, MD, PhD, Beth Israel Deaconess Medical Center, Harvard University
10:25 – 10:35	*Q&A*
10:35 – 11:05	**BREAK**
11:05 – 11:25	**Dynamic Disease Monitoring Network Biomarkers for Tracking Frontotemporal Dementia** William Seeley, MD, University of California, San Francisco
11:25 – 11:35	*Q&A*
11:35 – 11:55	**Behavioral Efficacy of Anti-Abeta42 Oligomer Small Molecules** Susan Catalano, PhD, Cognition Therapeutics, Inc.
11:55 – 12:05	*Q&A*
12:05 – 12:25	**Clinical Evaluation of MSDC-0160 in Subjects with Mild Alzheimer's Disease** Jerry R. Colca, PhD, Metabolic Solutions Development Company, LLC
12:25 – 12:35	*Q&A*
12:35 – 1:30	**LUNCH AND POSTER SESSION**
II. Neuroprotection: Synaptic Plasticity and Cognitive Enhancement Chair: Penny Dacks, PhD, Alzheimer's Drug Discovery Foundation	
1:30 – 1:35	**Session Overview: Penny Dacks, PhD, Alzheimer's Drug Discovery Foundation**
1:35 – 1:55	**Selective GABA a5 Ligands for Cognitive Enhancement in Patients with Mild Cognitive Impairment** Sharon Rosenzweig-Lipson, PhD, AgeneBio Inc.
1:55 – 2:05	*Q&A*
2:05 – 2:25	**Clinical Development of a Novel Activator of Phosphoprotein Phosphatase 2A for Alzheimer's Disease** Jeffry Stock, PhD, Signum Biosciences, Inc.
2:25 – 2:35	*Q&A*
2:35 – 2:55	**A New Treatment for Cognitive Disorders** Mauro Costa-Mattioli, PhD, Baylor College of Medicine
2:55 – 3:05	*Q&A*
3:05 – 3:35	**BREAK**
3:35 – 3:55	**In Vivo Characterization of Novel mGlu5 PAMs in Aged Rats** Jerri M. Rook, PhD, Vanderbilt Center of Neuroscience Drug Discovery
3:55 – 4:05	*Q&A*
4:05 – 4:25	**CRF1 Receptors as a Novel Target for Slowing Age-Related Neurodegeneration** John G. Csernansky, MD, Northwestern University
4:25 – 4:35	*Q&A*
4:35 – 4:55	**Two Novel Compounds for the Treatment of Alzheimer's Disease** Marguerite Prior, PhD, The Salk Institute
4:55 – 5:05	*Q&A*
5:05 – 5:10	**Closing Remarks** Howard Fillit, MD, Alzheimer's Drug Discovery Foundation
5:10 – 7:00	**NETWORKING RECEPTION AND POSTER SESSION**

Tuesday, September 11	
8:00 – 8:30	**Continental Breakfast**
8:30 – 9:10	**Plenary: Brain Bioenergetics and Aging: Therapeutic Strategies for Intervention** Russell H. Swerdlow, MD, University of Kansas School of Medicine
III. ApoE and Vascular Targets **Chair: Rachel Lane, PhD, Alzheimer's Drug Discovery Foundation**	
9:10 – 9:15	**Session Overview: Rachel Lane, PhD, Alzheimer's Drug Discovery Foundation**
9:15 – 9:35	**Optimizing Drug Like Compounds that Increase ApoE Release from Human Astrocytes to Treat Alzheimer's Disease** Rick Jack, PhD, Madera BioSciences, Inc.
9:35 – 9:45	*Q&A*
9:45 – 10:05	**Preventing Leukocyte Adhesion and Impaired Cerebral Blood Flow as a Treatment Strategy for Alzheimer's Disease** Nozomi Nishimura, PhD, Cornell University
10:05 – 10:15	*Q&A*
10:15 – 10:35	**Discovering Small Molecules to Increase Lipidation of ApoE** Cheryl Wellington, PhD, University of British Columbia
10:35 – 10:45	*Q&A*
10:45 – 11:10	**BREAK**
11:10 – 11:30	**Targeting ApoE and ApoE Receptor Pathways for Alzheimer's Disease Therapy** Guojun Bu, PhD, Mayo Clinic
11:30 – 11:40	*Q&A*
11:40 – 12:00	**Development of Peptidomimetic ApoE/Abeta Binding Inhibitors as an Effective and Non-Toxic Therapeutic Approach for AD** Thomas Wisniewski, MD, New York University School of Medicine
12:00 – 12:10	*Q&A*
12:10 – 12:30	**Identification of Small Molecules That Can Prevent Mitochondrial Dysfunction Associated with the Generation of Apolipoprotein E Fragments in Neurons** Robert W. Mahley, MD, PhD, The J. David Gladstone Institutes
12:30 – 12:40	*Q&A*
12:40 – 1:25	**LUNCH AND POSTER SESSION**
IV. Biomarkers to Accelerate Clinical Development **Chair: Howard Fillit, MD, Alzheimer's Drug Discovery Foundation**	
1:25 – 1:30	**Session Overview: Howard Fillit, MD, Alzheimer's Drug Discovery Foundation**
1:30 – 1:50	**Effects of Brain Beta-Amyloid on Postoperative Cognition** Marek Brzezinski, MD, PhD, University of California, San Francisco
1:50 – 2:00	*Q&A*
2:00 – 2:20	**Safety/Tolerability and Effects on Cognitive Impairment, Impaired Cerebral Cortical Metabolism and Oxidative Stress of R(+)Pramipexole Administered to Subjects with Early Alzheimer's Disease** James P. Bennett, Jr., MD, PhD, Virginia Commonwealth University
2:20 – 2:30	*Q&A*
2:30 – 2:50	**Imaging Agents for Diagnosis of Tauopathic Neurodegenerative Diseases** Jeff Kuret, PhD, Ohio State University
2:50 – 3:00	*Q&A*
3:00 – 3:20	**BREAK**
3:20 – 3:40	**[18F]-THK523, a Novel In Vivo Tau Imaging Agent** Victor L. Villemagne, MD, Austin Health
3:40 – 3:50	*Q&A*
3:50 – 4:10	**High Resolution Quantitative Magnetization Transfer Imaging in Entorhinal Cortex** Ying Wu, MD, NorthShore University Health System Research Institute
4:10 – 4:20	*Q&A*
4:20 – 4:40	**TDP-43 and Tau as Cerebrospinal Fluid Biomarkers to Discriminate Frontotemporal Dementia Subtypes** Marcel M. Verbeek, PhD, Radboud University Medical Center, Nijmegen
4:40 – 4:50	*Q&A*
4:50 – 5:00	**Closing Remarks** Howard Fillit, MD, Alzheimer's Drug Discovery Foundation

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The Alzheimer's Drug Discovery Foundation expresses its gratitude to the following supporters:

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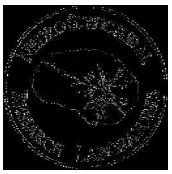

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2012 ADDF YOUNG INVESTIGATOR SCHOLARSHIPS

Congratulations to the recipients of the **ADDF Young Investigator Scholarships!** These scholarships recognize the early achievements of talented young investigators by offering them the opportunity to attend this conference and present posters of their work. Please visit the poster presentations during the breaks, lunch and networking reception.

The 2012 Young Investigator Scholars are:

Tao Ma, New York University - *New York, NY, United States*
Glucagon-like Peptide-1 Cleavage Product Glp-1 (9-36) Amide Rescues Synaptic Plasticity and Memory Deficits in Alzheimer Model

Antonett Madriaga, University of Illinois at Chicago - *Chicago, IL, United States*
Photoaffinity Labeling of Hdacs in Sh-sy5y Proteomes

Kelly Moore, University of South Carolina - *Columbia, SC, United States*
Inhibition of Alzheimer's-associated Abeta Aggregation by Gold Nanoparticles

Smita Mukherjee, University of Pittsburgh Medical School - *Pittsburgh, PA, United States*
A New Method for Quantifying The Chemical Heterogeneity of ABeta Peptides in Human Brain Using Immunoprecipitation in Combination with Liquid Chromatography/mass Spectrometric Analysis

Olalekan Ogundele, Bingham University College of Medicine - *Nassarawa, Nigeria*
Microtubule Polymerization Properties of Vitamin D3 (1, 25 Dihydroxy Cholecalciferol) in Fish Scale Melanocytes: A Model for the Study of Vitamin D3 in Mtpt Induced Parkinsonism.

Katie Robinson, University of Pennsylvania - *Phildelphia, PA, United States*
Characterization of Thromboxane Receptor-mediated Signaling: Insights into Novel Therapeutic Strategies for Alzheimer's Disease

Cristina Rodriguez-Rodriguez, University of British Columbia - *Vancouver, BC, Canada*
Thioflavin-based Multifunctional Molecules with Potential Dual Function as Diagnostic and Therapeutic Agents for Alzheimer's Disease

Kasturi Roy, Saha Institute of Nuclear Physics - *Kolkata, India*
Characterization of Aicd-grb2 Vesicle Trafficking

Isaac Schiefer, University of Illinois at Chicago - *Chicago, IL, United States*
Furoxans (1, 2, 5 Oxadiazole-n-oxides) as Novel No/cgmp/creb Signaling Neuroprotective and Procognitive Agents

Mitsuru Shinohara, Mayo Clinic - *Jacksonville, FL, United States*
Brain Regional Distribution of ABeta and Molecules or Markers Related To ABeta Metabolism in Non-demented Individuals

Shiri Stempler, Tel Aviv University School of Medicine - *Tel Aviv, Israel*
Prediction of Drug Targets in Alzheimer's Disease by Perturbations of Metabolic Networks

Maria Telpoukhovskaia, University of British Columbia - *Vancouver, BC, Canada*
Toward Development of Novel Chelators as Potential Drugs for Alzheimer's Disease

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FUNDING OPPORTUNITIES

2012 General Request for Proposals (RFP) and Funding Priorities

The Alzheimer's Drug Discovery Foundation's (ADDF) General RFP funds drug discovery and development research programs in the field of Alzheimer's disease, related dementias and cognitive aging in academic centers and biotechnology companies worldwide. Funding averages $150,000 per year and must be justified based on the scientific work plan. In some cases, multi-year proposals can be considered. *Next Deadline: October 10th (Letter of Intent (LOI) due prior to October 3rd)*

Program to Accelerate Clinical Trials (PACT) for Alzheimer's Disease

The ADDF has created the Program to Accelerate Clinical Trials (PACT) to increase the number of innovative drugs tested in humans at the crucial proof-of-concept stage for Alzheimer's disease. This program will fund biomarker-based pilot clinical trials for Alzheimer's disease. The ADDF will provide funding for up to $1,000,000 per application. *Next Deadline: October 10th (LOI due prior to October 3rd)*

2012 ADDF/ LBDA Lewy Body Dementia Biomarker Research Award

The ADDF and The Lewy Body Dementia Association (LBDA) are issuing an RFP for the 2012 ADDF/LBDA Lewy Body Dementia Biomarker Research Award. This award will provide selected programs with up to $100,000 for one year of support to catalyze a research project focused on developing innovative biomarkers that aid in early diagnosis, detection and disease monitoring of Lewy Body Dementia. *Deadline: October 10th (LOI due prior to October 3rd)*

Accelerating Drug Discovery for Frontotemporal Degeneration

Research investigating the pathologic mechanisms of neurodegeneration in frontotemporal dementias (FTD) and related disorders is advancing, creating new potential targets for drug discovery. The ADDF and The Association for Frontotemporal Degeneration (AFTD) seek to accelerate and support drug discovery for FTD and related disorders through this RFP. ADDF/AFTD will provide grants for one-year duration (up to $150,000 each) with the possibility of follow-on funding. *Deadline: September 20th (LOI due prior to September 13th)*

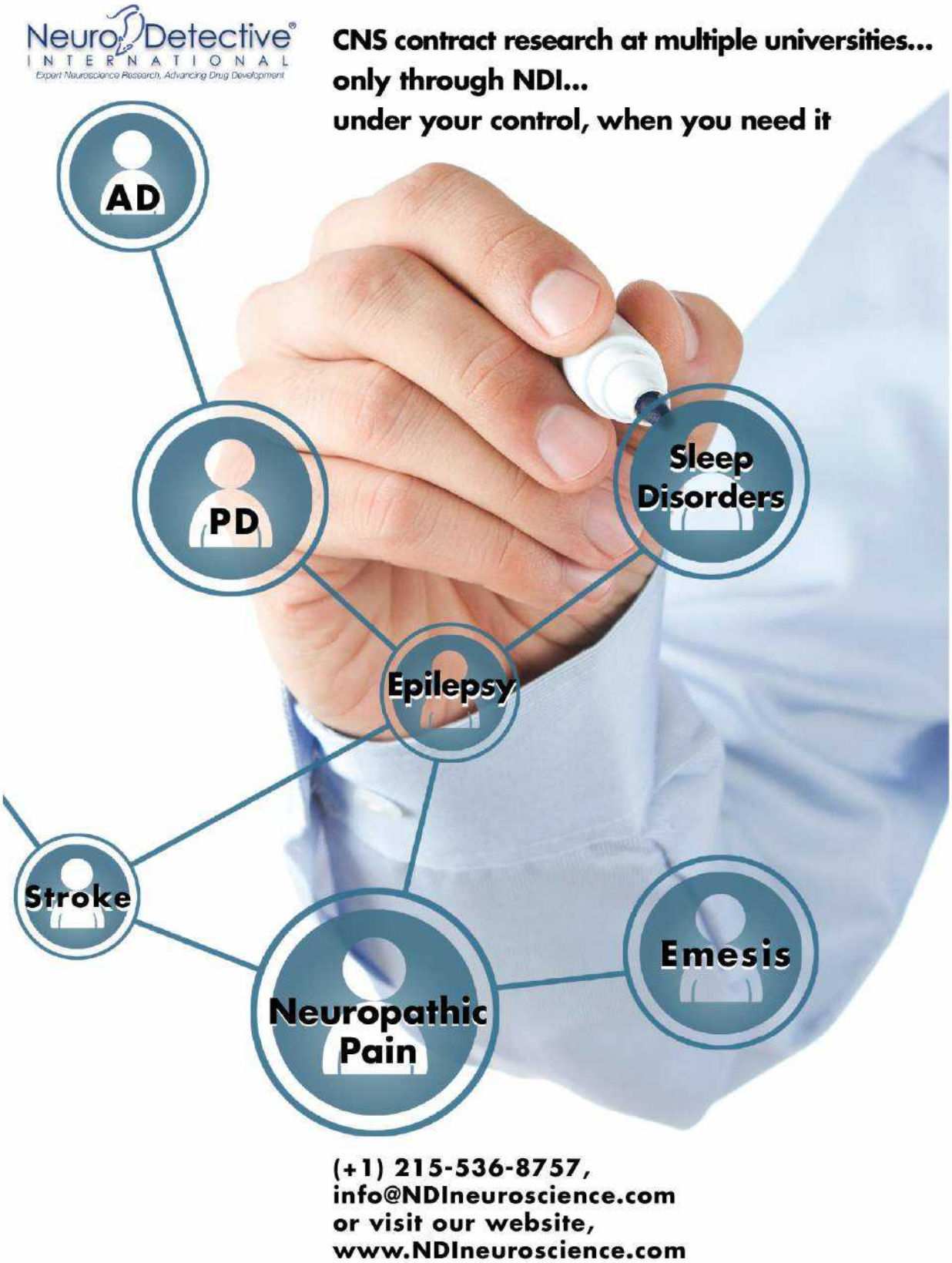
For more information or to apply for funding, please visit:
www.alzdiscovery.org/index.php/research-programs/grant-opportunities

For program related inquiries, please contact:

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

For application submission inquiries, please contact:

Niyati Thakker
Grants Manager
Phone: 212-901-8019
nthakker@alzdiscovery.org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BIOS AND ABSTRACTS

CONFERENCE CHAIR

Howard Fillit, MD, Alzheimer's Drug Discovery Foundation

Howard Fillit, MD, a geriatrician, neuroscientist and a leading expert in Alzheimer's disease, is the founding Executive Director of the Institute for the Study of Aging (ISOA), an Estée Lauder family foundation founded in 1998, and the Alzheimer's Drug Discovery Foundation (ADDF), an affiliated public charity founded in 2004. ISOA and ADDF share a common mission of accelerating drug discovery for Alzheimer's disease through venture philanthropy. Dr. Fillit has had a distinguished academic medical career at The Rockefeller University and The Mount Sinai School of Medicine where he is a clinical professor of geriatrics and medicine and professor of neurobiology. He was previously the Corporate Medical Director for Medicare at New York Life, responsible for over 125,000 Medicare managed care members in five regional markets. He is the author or co-author of more than 250 scientific and clinical publications, and is the senior editor of the leading international Textbook of Geriatric Medicine and Gerontology. Dr. Fillit has received several awards and honors including the *Rita Hayworth Award for Lifetime Achievement* from the Alzheimer's Association. He also serves as a consultant to pharmaceutical and biotechnology companies, health care organizations and philanthropies.

PLENARY SPEAKER

Michael Gold, **MS, MD,** Allon Therapeutics Inc.

Dr. Gold is Vice President, Clinical Development and Chief Medical Officer of Allon. Dr. Gold received his MD from the University of Miami Medical School and is board certified in neurology and psychiatry. Gold joins Allon directly from GlaxoSmithKline Inc. (GSK) where he most recently served as Vice-President, Neuroscience Medicines.

He has been an Assistant Professor of Neurology at the University of South Florida (USF) Medical School and Director of the USF Memory Disorders Clinic. In 1998, Gold joined Bristol-Myers Squibb in pharmacology and experimental medicine. He subsequently moved to Johnson & Johnson (J&J) in 2001 where he made significant contributions to the FDA approval of several compounds as well as being responsible for strategic development within the company's analgesia and neurodegeneration franchises.

Clinical Development of Neuroprotective Peptide, *Davunetide*

Michael Gold

Allon Therapeutics Inc., Vancouver, BC, Canada

Davunetide (AL-108) represents a highly innovative approach to the treatment of a variety of neurological or psychiatric disorders. Davunetide is believed to stabilize microtubules and thereby help neurons maintain both structural and functional integrity. The development of davunetide illustrates the challenges associated with a compound whose properties include: being a small peptide, having femtomolar potency, having activity across a broad range of pre-clinical models, not having an identified cognate receptor and having pleotropic effects. These challenges need to be understood in the context of emerging data that treatments focused on a single mechanism of action are unlikely to be effective in treating these devastating disorders.

I. Neuroprotection: Aβ, Tau, and Mitochondria Function

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

Orally Active Bioavailable Metal Attenuating Compounds for Alzheimer's Disease
Peter F. Kador, PhD, University of Nebraska Medical Center

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Susan Catalano, PhD, Cognition Therapeutics, Inc.

Clinical Evaluation of MSDC-0160 in Subjects with Mild Alzheimer's Disease
Jerry R. Colca, PhD, Metabolic Solutions Development Company, LLC

SESSION CHAIR

Diana Shineman, PhD, Alzheimer's Drug Discovery Foundation

Diana Shineman, PhD, is Director, Scientific Affairs at the Alzheimer's Drug Discovery Foundation, where she is responsible for developing and managing all aspects of the Foundation's drug discovery research programs. Dr. Shineman earned her PhD in Cell and Molecular Biology from the University of Pennsylvania (Penn). At Penn's 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, the Association for Women in Science and an author on numerous peer-reviewed publications.

Peter F. Kador, PhD, University of Nebraska Medical Center

Peter F. Kador received a PhD in Medicinal Chemistry from the Ohio State University in 1976. Starting as a Staff Fellow at the National Eye Institute, National Institutes of Health, he was promoted to Research Chemist in 1979, Head of the Section of Molecular Pharmacology in 1985 and Chief of the Laboratory of Ocular Therapeutics in 1991. For the last ten years, Dr. Kador has served as Professor in the College of Pharmacy of the University of Nebraska Medical Center and holds appointments in the Department of Ophthalmology and School of Veterinary Medicine and Biomedical Sciences at the University of Nebraska Lincoln. He is also President and CEO of Therapeutic Vision, Inc., a startup company that is currently developing (Phase 3) KinostatTM, a topical eye drop, for the treatment of cataracts in diabetic dogs. Dr. Kador has published extensively on the aldose reductase enzyme and its inhibitors, and their role in diabetic complications of the eye; age-related cataracts and anti-cataract agents; diabetic retinopathy; and the use of MRI and NMR spectroscopy as a non-invasive tool for eye research. He has developed and characterized a number of animal models and established that the galactose-fed dog is the only animal model that demonstrates both clinical as well as histological retinal changes similar to man. Currently, Dr. Kador is investigating cell signaling changes during the onset of cataract and retinopathy, and he has designed and synthesized multifunctional antioxidants to treat age-related degenerative diseases of the eye and neural tissues including Alzheimer's disease.

Dr. Kador serves as the Executive Vice-President for the National Foundation for Eye Research, has served as President of the Association for Ocular Pharmacology and Therapeutics and currently serves as a trustee. He has organized or co-organized over twenty-five National and International Workshops and Conferences, has 220 publications and 6 patents.

Orally Active Bioavailable Metal Attenuating Compounds for Alzheimer's Disease

Peter F. Kador[1,2], Hiroyoshi Kawada, James Randazzo, Zifeng Zhang and Karen Blessing[1,2]

[1]Pharmaceutical Sciences, University of Nebraska Medical Center, [2]Therapeutic Vision, Inc., Omaha, NE, USA

Oxidative stress, metalloprotein redox reactions, Aβ molecular pathology, and inflammation all contain some mechanism(s) of radical reaction that have been implicated in the pathogenesis of age-related diseases such as cataract, atrophic AMD, and neurodegenerative Alzheimer's Dementia. Using the innovative therapeutic approach that multifunctional metal attenuating antioxidants targeting two (or more) mechanisms of radical action are superior to compounds only addressing a single mechanism, we have synthesized a new class of multifunctional antioxidants (MFAOs) possessing a novel 2-amino-5-hydroxyl pyrimidine radical scavenging system (FRS) that not only is able to independently quench free radicals but also selectively chelate redox active iron. *In vitro* cell culture studies with SRA1 human lens epithelial cells, ARPE-19 human retinal pigmented epithelial cells, RGC-5 retinal ganglion cells, and SH-SY5Y neuroblastoma cells demonstrate that these compounds protect against both peroxide radicals and Fenton generated hydroxyl radicals. When orally administered select MFAOs can attain therapeutic levels in the brain, lens, and retina. In proof of concept studies in the eye these MFAOs delay cataract formation induced by exposure to whole head gamma irradiation, UV light, and diabetes and light-induced retinal degeneration. Bioavailability studies suggest that distinct molecular descriptors calculated for each compound may be useful in defining the targeted uptake of these MFAOs to target tissues in the eye versus the brain.

Supported by NIH EY016460, a grant from Therapeutic Vision Inc., and Alzheimer's Drug Discovery Foundation. Grant No. 20110702

Kun Ping Lu, MD, PhD, Beth Israel Deaconess Medical Center, Harvard University

Kun Ping Lu, M.D, PhD received his medical training in China and PhD degree from Duke University, followed by postdoctoral training at the Salk Institute. Dr. Lu was recruited as Assistant Professor in 1996, promoted to Associate Professor in 2001 and then to Full Professor in 2008 at Harvard Medical School. Dr. Lu research focuses on the role and regulation of cell proliferation and telomere maintenance and their role in the development and treatment of human disease. Dr. Lu identified many new human genes, including the prolyl isomerase Pin1 and telomeric protein Pin2/TRF1 and telomerase inhibitor PinX1. Dr. Lu laboratory has discovered that Pin1 is a unique enzyme that regulates protein conformation after phosphorylation, thereby leading to a novel concept of post-phosphorylation regulation in cell signaling. His work has established a new paradigm in cell signaling in physiology and pathology and also points to potentially novel therapeutic strategies in maladies as diverse as cancer, inflammation, autoimmune disorders, and Alzheimer's disease. For example in Alzheimer's disease, Pin1 plays a critical role in protecting against age-dependent tau- and Abeta-related pathologies and neurodegeneration by preventing the accumulation of the pathological protein conformations. This opens attractive new ideas for early diagnosis and treatment of AD and other Pin1-related diseases.

Development and Efficacy Evaluation of Novel Immunotherapy for Human Tauopathies

Kun Ping Lu

Beth Israel Deaconess Medical Center, Harvard University, Boston, MA, USA

The neuropathological hallmark of human tauopathies including AD are tangles made of phosphorylated tau (p-tau). It has been shown that toxic tau can spread and transmit tau pathology between neurons and that active or passive immunization against p-tau shows promise in mouse models, but how to target specifically the early pathogenic p-tau conformation in MCI and AD is still not clear. We have recently found that the phosphorylated Thr231-Pro motif in tau (pT231-tau) exists in the two distinct conformations, *cis* and *trans,* and identified a unique enzyme, Pin1, to accelerate its *cis* to *trans* conversion, thereby inhibiting tangle formation. We have now developed novel peptide chemistry to generate antibodies that specifically recognize *cis* or *trans* pT231-tau and demonstrated that *cis*, but not *trans,* pT231-tau is the early pathogenic conformation in MCI and AD. We have been testing our novel hypotheses that vaccines or antibodies that are specifically against the pathogenic *cis* pT231-tau conformation might be effective and specific in treating MCI and early AD patients and that assaying such *cis* tau conformation in CSF might help identify the patients for the novel therapies. We have used our novel peptide chemistry to develop conformation-specific vaccines and monoclonal antibodies specifically against *cis* and *trans* pT231-tau. We will compare the efficacy of these *cis* and *trans* pT231-tau conformation-specific vaccines and monoclonal antibodies in inhibiting or preventing p-tau pathological conformations, tau pathologies and neurodegeneration, and cognitive deficits in AD mouse models.

William Seeley, MD, University of California, San Francisco

Dr. Seeley attended medical school at the University of California at San Francisco (UCSF), where he first encountered patients with frontotemporal dementia (FTD) in 1999, during a research elective with Dr. Bruce Miller. He then completed a neurology residency at Harvard Medical School, training at the Massachusetts General and Brigham & Women's Hospitals. Returning to UCSF for a behavioral neurology fellowship, with Dr. Miller, Dr. Seeley developed expertise in the differential diagnosis and treatment of patients with neurodegenerative disease. He is currently an Associate Professor of Neurology at the UCSF Memory and Aging Center, where he participates in patient evaluation and management. Dr. Seeley's research in his Selective Vulnerability Research Laboratory concerns regional vulnerability in dementia, that is, why particular dementias target specific neuronal populations. Dr. Seeley addresses this question through behavioral, functional imaging and neuropathology studies. The goal of his research is to determine what makes brain tissues susceptible or resistant to degeneration, with an eye toward ultimately translating these findings into novel treatment approaches.

Dynamic Disease-Monitoring Network Biomarkers for Tracking Frontotemporal Dementia

William Seeley

University of California, San Francisco, San Francisco, CA, USA

Drug discovery relies on robust and sensitive methods for measuring treatment efficacy. Most neurodegenerative disease clinical trials have employed coarse clinical-functional outcome measures that are several steps removed from neuronal integrity. Neuroimaging studies provide a potential solution by directly quantifying the status of the target organ. Morphometric MRI and PET imaging have been the most extensively studied, but each of these methods has notable drawbacks. We have begun to pursue intrinsic connectivity network (ICN) functional MRI as a disease-tailored treatment monitoring strategy. In this presentation, I will present emerging longitudinal ICN findings from patients with frontotemporal dementia, Alzheimer's disease, and related disorders.

Susan Catalano, PhD, Cognition Therapeutics, Inc.

Dr. Catalano received her BA from Barnard College and PhD from University of California, Irvine, and did postdoctoral training at University of California, Berkeley, and Caltech in the field of neurobiology. While a scientist at Roche Palo Alto, she led Neurophysiology and Neuroimaging groups and an exploratory program in psychiatric disorders. Following this, Dr. Catalano joined Rigel Pharmaceuticals, Inc. and led the team that discovered Aurora kinase inhibitor R763 currently in clinical trials. Dr. Catalano founded a successful consulting practice, Drug Discovery Imaging, and then served as Director of Discovery Biology for Acumen Pharmaceuticals, Inc. Dr. Catalano founded Cognition Therapeutics Inc. in 2007 to discover drugs to treat or prevent Alzheimer's disease and currently serves as its Chief Science Officer. The company is currently advancing its candidate drugs towards the clinic. *www.cogrx.com*

Behavioral Efficacy of Anti-Abeta42 Oligomer Small Molecules

Susan Catalano, N. Izzo, C. Rehak, R. Yurko, K. Mozzoni, C. Silky, G. Look, G. Rishton, H. Safferstein

Cognition Therapeutics, Inc., Pittsburgh, PA, USA

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 first-in-class receptor antagonists that block the toxic effects of Abeta oligomers by binding with high affinity to CNS receptors, reducing Abeta oligomer binding to neurons, competing with oligomers for receptors/proteins regulating membrane trafficking rate, eliminating Abeta oligomer-induced abnormal membrane trafficking, and eliminating Abeta oligomer-induced synapse loss/regression. Molecules from two structurally distinct series have demonstrated prevention of Abeta oligomer-induced associative memory failure in an acute AD model (Abeta 1-42 oligomer injection in wild-type mouse brain) as measured by fear conditioning, and reversal of memory failure in both genders of a transgenic animal model at nanomolar brain concentrations following shorter duration of treatment than previously published therapeutics. They exhibit a high brain/plasma ratio following long term administration and no behavioral toxicity, as well as no neurotoxicity or glial toxicity in vitro. The receptor antagonist mechanism of action will allow the design of disease-modifying therapeutic clinical trials based on receptor occupancy at critical receptor binding sites together with cognitive outcome.

Supported by Cognition Therapeutics Inc., NIA #AG037337, ADDF #20100501

Jerry R. Colca, PhD, Metabolic Solutions Development Company, LLC

Jerry R. Colca, PhD, is a co-founder, part owner, and President/Chief Scientific Officer of Metabolic Solutions Development Company (MSDC; msdrx.com) in Kalamazoo, MI. Jerry has spent his professional career studying the endocrine control of metabolism as relates to diabetes. He has a BS in Biology and MS and PhD in Physiology and Biochemistry from the University of Houston where he studied the regulation of secretion of pancreatic hormones. His post-doctoral training at Washington University concentrated on the biochemistry of isolated pancreatic islets and the study of stimulus-secretion coupling in the control of metabolism. Jerry joined the Upjohn Company in 1984 to study to the mechanism of action of the thiazolidinediones and was instrumental in selection and development of pioglitazone hydrochloride (Actos®) as an anti-diabetic agent through Phase 2A clinical studies. The company formally known as Upjohn exited the insulin-sensitizing field in 1993. Jerry remained with the Upjohn Company through the mergers with Pharmacia, Monsanto-Searle, and Pfizer until he retired from the merged company in 2005. During this time he was leader of diabetes discovery team in Kalamazoo, helped build a new diabetes discovery effort in Sweden after the merger with Pharmacia, and finally building a new targets discovery effort in St. Louis after the Pfizer merger. Jerry has been interested in the mechanism of action of the insulin sensitizer TZDs from the early days of their discovery and especially in the safety and pharmacology of pioglitazone. In January of 2006, Jerry co-founded MSDC with Dr. Rolf Kletzien to take advantage of their unique insight into these molecules. The company has now grown to have two compounds in clinical trials and is making significant progress into understanding the molecular mechanisms of the insulin sensitizers.

Clinical Evaluation of MSDC-0160 in Subjects with Mild Alzheimer's Disease

Jerry R. Colca

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

There is a growing understanding that there is a connection between insulin resistance/diabetes and Alzheimer's disease. Of particular interest, the pathology of both diseases includes mitochondrial dysfunction. We have recently focused on the action of insulin sensitizers that involves a previously unrecognized mitochondrial membrane complex containing a protein that we call mTOT (mitochondrial Target of Thiazolidinediones), which we identified by drug analog crosslinking and proteomics. We have demonstrated that modifications could be made in molecules of structure similar to the anti-diabetic therapeutic, pioglitazone, which reduced the ability to bind to and activate a transcription factor, PPARg, but which maintains the mTOT interaction. We believe the activation of PPARg drives the off-target side effects, while useful pharmacology is mediated through mTOT. The first PPAR-sparing compound, MSDC-0160, has recently completed phase 2B trial in type 2 diabetic subjects, which shows that MSDC-0160 can lower glucose similar to pioglitazone but with reduced off-target issues. We have also shown that this compound can reduce brain inflammation and the size and number of plaques in a mouse model of Alzheimer's disease. Based on all of these observations, we have initiated a clinical study of MSDC-0160 in subjects with mild Alzheimer's disease. This study (NCT01374438) is currently underway and is comparing 90 days of treatment with MSDC-0160 (once daily) against placebo in a randomized, blinded trial. The main endpoints are change in brain glucose utilization using FDG-PET with pre-specified regions of interest analysis together with various measures of cognitive and executive function. I will discuss the current status of this trial together with the recent understandings of this new mechanism of action.

II. Neuroprotection: Synaptic Plasticity and Cognitive Enhancement

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

Selective GABA a5 Ligands for Cognitive Enhancement in Patients with Mild Cognitive Impairment
Sharon Rosenzweig-Lipson, PhD, AgeneBio Inc.

Clinical Development of a Novel Activator of Phosphoprotein Phosphatase 2A for Alzheimer's Disease
Jeffry Stock, PhD, Signum Biosciences, Inc.

A New Treatment for Cognitive Disorders
Mauro Costa-Mattioli, PhD, Baylor College of Medicine

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

CRF1 Receptors as a Novel Target for Slowing Age-Related Neurodegeneration
John G. Csernansky, MD, Northwestern University

Two Novel Compounds for the Treatment of Alzheimer's Disease
Marguerite Prior, PhD, The Salk Institute

SESSION CHAIR

Penny Dacks, PhD, Alzheimer's Drug Discovery Foundation

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

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

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

Sharon Rosenzweig-Lipson, PhD, AgeneBio Inc.

Dr. Sharon Rosenzweig-Lipson is currently Vice President of Research for AgeneBio and Adjunct Professor of Pharmacology and Physiology at Drexel University. She has 20 years of experience developing compounds for Psychiatric and Neurologic indications in the pharmaceutical industry (American Cyanamid – American Home Products – Wyeth – Pfizer). During that time her laboratory focused on developing novel therapies for depression, anxiety, schizophrenia and cognitive dysfunction. She has served in multiple roles including Head of In Vivo for Depression/Anxiety and Schizophrenia and Head of Translational Neuroscience. Dr. Rosenzweig-Lipson has successfully led teams from the earliest exploratory studies through to Phase II Proof of Concept Trials. In 2011, she founded IVS Pharma Consulting LLC to bring her expertise in in screening strategies, in vivo models, translation and early clinical development strategy to the Neuroscience Scientific Community in Pharma, Biotech and Academia. She has authored 70 articles and book chapters and is an inventor on 13 issued patents. Dr. Rosenzweig-Lipson received her BA in the Biological Basis of Behavior from the University of Pennsylvania and her PhD in Psychology (Behavioral Neuroscience) from Harvard University.

Selective $GABA_A$ α5 Ligands for Cognitive Enhancement in Patients with Mild Cognitive Impairment

Sharon Rosenzweig-Lipson, Ming Teng Koh, Michela Gallagher

AgeneBio, Carmel, IN, USA

A condition of excess activity in the hippocampal formation is observed in the aging brain and in conditions that confer additional risk during aging for Alzheimer's disease. Compounds that act as positive allosteric modulators at $GABA_A$ α5 receptors might be useful in targeting this condition because $GABA_A$ α5 receptors mediate tonic inhibition of principal neurons in the affected network. While agents to improve cognitive function in the past focused on inverse agonists, which are negative allosteric modulators at $GABA_A$ α5 receptors, research supporting that approach used only young animals and predated current evidence for excessive hippocampal activity in age-related conditions of cognitive impairment. Compounds with functional activity as potentiators of γ-aminobutyric acid at $GABA_A$ α5 receptors were evaluated for their ability to improve hippocampal-dependent memory in aged rats with identified cognitive impairment. Improvement was obtained in aged rats across protocols differing in motivational and performance demands and across varying retention intervals. Significant improvement occurred after either intracereboventricular infusion or systemic administration. Furthermore, systemic administration improved behavioral performance at dosing shown to provide drug exposure in the brain and in vivo receptor occupancy in the hippocampus. A medicinal chemistry program has been initiated to identify potent and selective $GABA_A$ α5 positive allosteric modulators for the treatment of amnestic MCI. These data suggest a novel approach to improve neural network function in clinical conditions of excess hippocampal activity.

Jeffry Stock, PhD, Signum Biosciences, Inc.

Jeffry Stock, PhD, a tenured full professor in the departments of Molecular Biology and Chemistry at Princeton University, is one of the world's leading experts in signal transduction and global cellular regulation with over 150 original scientific articles in the area. He is an elected fellow of the American Society of Microbiology and a winner of the Humboldt Prize. He is on the editorial boards of the *Journal of Biochemistry* and *BMC Microbiology*, and he serves on the Centers Review Committee for the National Institute of Drug Abuse. Professor Stock is best known for his seminal work on the biochemistry of signal transduction in microorganisms. He discovered both the system that regulates PP2A to control the cellular phosphoregulatory networks in higher organisms and the CAAX-tail modification system that globally regulates Ras and other G-Proteins involved in signal transduction.

Clinical Development of a Novel Activator of Phosphoprotein Phosphatase 2A for Alzheimer's Disease

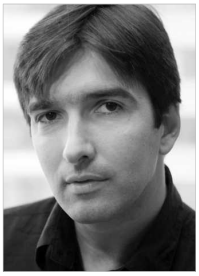
Jeffry Stock

Signum Biosciences, Inc., Monmouth Jct, NJ, USA

Therapeutic targets for Alzheimer's disease that act in critical pathways at the core of the disease process are needed for novel treatment strategies. The pathway of tau hyperphosphorylation is intimately linked to disease pathobiology, resulting in the characteristic hallmark neurofibrillary tangles, contributing to neurodegeneration and being a strong biomarker for disease progression. We have been investigating the primary enzyme that dephosphorylates tau, Phosphoprotein Phosphatase 2A (PP2A), as a target to modulate tau's phosphorylation state and thus prevent, or halt, disease progression. A specific post-translational modification, carboxyl methylation, acts to regulate the assembly of a subset of PP2A that acts on specific substrates including tau. By inhibiting the demethylation of PP2A, through PP2A methylesterase (PME1), an enzyme that only acts on this phosphatase, assembly of this specific PP2A isoform is promoted, therefore enhancing tau dephosphorylation. Furthermore, PP2A methylation status has been demonstrated to be reduced in brains of Alzheimer's disease patients, further linking the relevance of this modification to disease.

Through screening of botanical extracts we identified a PP2A demethylation inhibitory activity in coffee, which we refined to develop an optimized extract, CognionTM. Study of the active component of CognionTM, demonstrate that it can safely and efficaciously modulate relevant biochemical and behavioral endpoints in models of Alzheimer's disease. In a brain slice model it reduces tau phosphorylation and acts as a neuroprotectant. In vivo, modulation of PP2A demethylation can reduce tau related abnormalities and lead to improved motor and cognitive performances. The advancement of this novel PP2A activator therefore provides a rapid and promising path for clinical development.

Mauro Costa-Mattioli, PhD, Baylor College of Medicine



Mauro Costa-Mattioli received his bachelor's degree in biology from the Faculty of Science (University of the Republic, Montevideo, Uruguay). In 1998, he received his master's degree (Diplôme Universitaire) from Pierre and Marie Curie University (Paris) and his PhD from the University of Nantes (Nantes). In his graduate work he studied virology and immunity. In 2002, he joined the laboratory of Dr. Nahum Sonenberg, at McGill University (Montreal) as post-doctoral fellow. His work defined the role of translational (protein synthesis) control in long-lasting synaptic plasticity and memory formation. In 2008, he joined the faculty at Baylor College of Medicine in Houston, Texas as an Assistant Professor of Neuroscience and Molecular and Cellular Biology. Using multidisciplinary approaches Dr. Costa-Mattioli's laboratory studies the molecular and cellular mechanisms underlying long-term synaptic plasticity, learning and memory and related neurological disorders. Mauro has received several awards, including the Science & Eppendorf International Award, and the Searle Scholar award.

A New Treatment for Cognitive Disorders

Mauro Costa-Mattioli

Baylor College of Medicine, Houston, TX, USA

How memories are stored in the brain is a question that has intrigued mankind over many generations. While neuroscientists have already made great strides, indentifying key brain regions and relevant neuronal circuits, many questions regarding the specialized molecular and neuronal mechanisms underlying memory formation remain unanswered. Post-translational modifications of synaptic proteins could explain transient synaptic processes, such as short-term memory (STM) and the early phase of LTP (E-LTP, lasting 1-3 hours), but new protein synthesis is required for long-lasting ones, such as LTM and the late phase of LTP (L-LTP, lasting several hours). I will focus on our recent findings: a novel signaling pathway that regulates the conversion from short- to long-term memory, brain rhythmicity and L-LTP.

Jerri M. Rook, PhD, Vanderbilt Center of Neuroscience Drug Discovery

Dr. Rook is an Assistant Professor of Pharmacology at Vanderbilt University in the Vanderbilt Center for Neuroscience Drug Discovery. Dr. Rook received her PhD degree in Pharmacology from the University of Kansas Medical Center in 2008 where she was supported by the KUMC Biomedical Research Training Program Award. She then pursued her postdoctoral studies in the laboratory of P. Jeffrey Conn, PhD at Vanderbilt University before being promoted to Assistant Professor. Dr. Rook has served as an author on several primary research articles in peer-reviewed scientific journals and frequently presents her work at both national and international meetings. She is currently the member of the American Society for Pharmacology and Experimental Therapeutics and Society for Neuroscience. Dr. Rook has received multiple awards including the Ruth L. Kirschstein National Research Service Award from the National Institute of Mental Health in 2009 and is the recent recipient of The Alzheimer's Drug Discovery Foundation and Charles River Laboratories International, Inc. 2011 partnership award program to accelerate the discovery of new drugs for cognitive aging and Alzheimer's disease.

In Vivo Characterization of Novel mGlu5 PAMs in Aged Rats

Jerri M. Rook

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

Alzheimer's disease (AD) is the most common form of dementia and is characterized by the progressive decline in cognitive function, with the primary deficits being hippocampal-mediated learning and memory loss. Recent studies suggest the involvement of glutamate in the pathology of the disease, as levels are decreased in the hippocampus of patients with AD. Glutamate modulates excitatory postsynaptic currents via metabotropic glutamate receptor. Metabotropic glutamate receptor subtype 5 ($mGlu_5$) is the most highly expressed mGlu in the hippocampus and is a close signaling partner of the N-methyl-D-aspartate receptor (NMDAR). NMDAR is critical in regulating hippocampal synaptic plasticity and essential for hippocampal-dependent cognitive function. Therefore, increased activation of $mGlu_5$ offers an exciting new therapeutic strategy to enhance cognitive function in patients suffering from AD. Recently, our group has developed a series of highly potent, selective $mGlu_5$ positive allosteric modulators (PAMs) with enhanced physiochemical and pharmacokinetic properties for *in vivo* studies, providing an unprecedented opportunity to evaluate the potential of selective potentiation of $mGlu_5$ as a novel target for the treatment of symptoms associated with AD. As opposed to direct activation of $mGlu_5$, PAMs dramatically potentiate the response of the receptor to its endogenous ligand glutamate and offer high selectivity while avoiding unwanted side effects seen with direct activation. Aged rats have a loss of hippocampal synaptic function as well as cognitive function and provide a preclinical animal model that accurately emulates the human disease state. These studies utilize the aged rat model to characterize the ability of our novel $mGlu_5$ PAMs to restore the deficits associated with impaired cognitive function observed in AD.

John G. Csernansky, MD, Northwestern University

Dr. Csernansky currently serves as the Lizzie Gilman Professor and Chair in the Department of Psychiatry and Behavioral Sciences at Northwestern University Feinberg School of Medicine. Prior to coming to Northwestern, Dr. Csernansky served as the Gregory B. Couch Professor of Psychiatry at Washington University School of Medicine, and secured NIH funding there to establish a Conte Center for the Neuroscience of Mental Disorders, which was focused on improving our understanding of the neurodevelopmental origins of schizophrenia. His research interests include *in vivo* neuroimaging of neuropsychiatric disorders, especially schizophrenia and Alzheimer's disease, clinical trials of cognition-enhancing drugs, and the development of valid animal models for neuropsychiatric disorders.

Dr. Csernansky has over 250 peer-reviewed publications, and has also authored several chapters and books, and his research program has received grant support from the National Institute of Mental Health, the National Institute of Aging, and the Department of Veterans Affairs, as well as several foundations and pharmaceutical companies. He is a Fellow of the American Psychiatric Association and the American College of Neuropsychopharmacology, and a member of several other professional societies, including the Society for Neuroscience and the Society of Biological Psychiatry. He has served as an Associate Editor of Schizophrenia Bulletin and on the Editorial Board of Neuropsychopharmacology.

CRFR1 as a Novel Target for Slowing Age-Related Neurodegeneration

John G. Csernansky and Hongxin Dong

Northwestern University, Evanston, IL, USA

There is a growing consensus that environmental factors, such as psychosocial stress, can accelerate the progression of Alzheimer's disease (AD). Over the last ten years, we have investigated the links between psychosocial stressors, amyloid plaque deposition and cognitive decline in both animal models of AD and in patients with AD. Early experiments using Tg2576 mice showed that chronic isolation stress increased tissue levels of Abeta, and accelerated amyloid plaque deposition and the progression of memory-related behavioral deficits. Using an *in vivo* microdialysis in Tg2576 mice, and primary cultures of neurons from Tg2576 mice, we then found that corticotropin releasing factor (CRF) can mimic the effects of stress by increasing the production of Abeta. More recently, we have also shown that depolarization blockers, such as TTX, and antagonists at the CRF type 1 receptor (CRFR1), such as antalarmin, can block the effects of both stress and CRF in Tg2576 mice. Currently, we are investigating the effects of CRFR1 antagonists on other age-related processes in aged rats. The results of these experiments will allow us to evaluate the promise of CRFR1 antagonist for slowing the progression of cognitive decline in older adults with and without AD.

Marguerite Prior, PhD, The Salk Institute

Dr. Marguerite Prior joined the Cellular Neurobiology Laboratory of Professor David Schubert at the Salk Institute in May 2010 as a Postdoctoral Research Associate. Dr. Prior received her Ph.D. from University College Dublin, Ireland in 2007, working on Prion Diseases under the direction of Dr. Hillary McMahon. She began her postdoctoral training as a research fellow in the department of Neuroscience at the Lerner Research Institute, Cleveland Clinic under the direction of Dr. Riqiang Yan, an expert in the Alzheimer's field relating to both the BACE enzyme and the role of reticulon proteins in the formation of dystrophic neurites. During this time she received a fellowship from the Alzheimer's Health Assistance Foundation (AHAF) to investigate the relationship between plaques and dystrophic neurites. Following the completion of this project she moved to Professor Schubert's lab in La Jolla to work on a novel neurotrophic and cognitive enhancing drug for Alzheimer's disease. Dr. Prior has received two young investigator scholarships from the ADDF in the past and is currently funded through an award from the ADDF.

Two Novel Compounds for the Treatment of Alzheimer's Disease

Marguerite Prior

The Salk Institute, San Diego, CA, USA

At present, there are few drugs that improve the memory deficits associated with normal aging and none that prevent cognitive decline in chronic neurodegenerative conditions such as Alzheimer's disease (AD), which is the most common cause of dementia in the elderly affecting more than 24 million people worldwide. Historically, the search for a treatment for AD has been focused on the amyloid beta peptide (Aβ) that mediates familial Alzheimer's disease pathology. However, given that age is the greatest risk factor for AD, our laboratory has explored an alternative drug discovery paradigm to select drug candidates for neurodegenerative disease that is based on efficacy in cell models of multiple age-associated pathologies rather than exclusively amyloid metabolism. This scheme has identified an exceptionally potent, orally active, neurotrophic compound (J147) that facilitates memory in normal rodents, prevents behavioral and synaptic protein loss in AD transgenic mice, and reverses cognitive loss in aged transgenic AD mice. J147 is also neurogenic in both very old and young mice and reduces the significant loss in dendritic spines that occurs with age. Strikingly, we have found that the neurotrophic and memory-enhancing activities of J147 are associated with the induction of brain derived neurotrophic factor (BDNF), a growth factor that is reduced with age and in AD brain, that is required for normal cognitive function, and is implicated in neurogenesis. J147 has the medicinal chemical properties of a good CNS drug and our data so far suggests that J147 has potential for the treatment of AD. However, in order to have a backup compound for J147, we have recently been generating some derivatives of J147 using SAR driven chemistry. One derivative of J147 with similar potency but superior pharmacological properties is currently being tested in AD transgenic mice for its ability to reverse AD behavior and pathology.

PLENARY SPEAKER

Russell H. Swerdlow, MD, University of Kansas School of Medicine

Dr. Russell Swerdlow is a physician-scientist at the University of Kansas. He directs the NIA-supported University of Kansas Alzheimer's Disease Center and holds appointments in the departments of Neurology, Physiology, and Biochemistry and Molecular Biology. He received his undergraduate and doctor of medicine degrees from New York University, and trained as a neurologist and neuroscientist at the University of Virginia. He is a recipient of an S. Weir Mitchell Award from the American Academy of Neurology, a Cotzias Award from the American Parkinson's Disease Foundation, a Scholarly Research Award from the University of Kansas, and multiple grant awards from the National Institutes of Health. He has served as the Research Committee Chair of the CurePSP Foundation, chaired the Commonwealth of Virginia Alzheimer's Disease Commission, and sits on the editorial board of several research journals including Neurology and the Journal of Alzheimer's Disease. Dr. Swerdlow's main research focus includes studies of brain energy metabolism and the role brain energy metabolism plays in brain aging, Alzheimer's disease, and other neurodegenerative diseases. His laboratory is currently developing approaches to manipulate brain energy metabolism. The goal of this work is to create new and effective treatments that will hopefully help people with Alzheimer's disease.

Brain Bioenergetics and Aging: Therapeutic Strategies for Intervention

Russell H. Swerdlow

University of Kansas School of Medicine, Kansas City, KS, USA

Bioenergetic changes occur in the aging brain and to an even greater extent in Alzheimer's disease (AD). Bioenergetic perturbations, it is argued, could represent a molecular link between these two states, with the magnitude of the perturbation defining a boundary between normal and AD-associated brain aging. Evidence also suggests AD bioenergetic dysfunction originates at least to some extent from within mitochondria, and a "mitochondrial cascade hypothesis" has been proposed that postulates mitochondrial dysfunction initiates and drives neurodysfunction, neurodegeneration, and histology changes in late-onset AD. If correct, mitochondrial medicine approaches may offer unique opportunities for promoting brain health during aging and for treating AD. While the field of mitochondrial medicine was defined several decades ago, new insights into cell bioenergetics, how it changes in the aging and AD brain, and how to manipulate bioenergetic physiology is now helping to identify new mitochondrial medicine strategies.

III. ApoE and Vascular Targets

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

Optimizing Drug Like Compounds that Increase ApoE Release from Human Astrocytes to Treat Alzheimer's Disease
Rick Jack, PhD, Madera BioSciences, Inc.

Preventing Leukocyte Adhesion and Impaired Cerebral Blood Flow as a Treatment Strategy for Alzheimer's Disease
Nozomi Nishimura, PhD, Cornell University

Discovering Small Molecules to Increase Lipidation of ApoE
Cheryl Wellington, PhD, University of British Columbia

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

Development of Peptidomimetic ApoE/Abeta Binding Inhibitors as an Effective and Non-Toxic Therapeutic Approach for AD
Thomas Wisniewski, MD, New York University School of Medicine

Identification of Small Molecules That Can Prevent Mitochondrial Dysfunction Associated with the Generation of Apolipoprotein E Fragments in Neurons
Robert W. Mahley, MD, PhD, The J. David Gladstone Institutes

SESSION CHAIR

Rachel Lane, PhD, Alzheimer's Drug Discovery Foundation

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

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

Rick Jack, PhD, Madera Biosciences Inc.

Dr. Rick Jack has more than 15 years of drug discovery research and development experience in both biotech and pharma environments. He is a scientific co-founder of Madera and is its President and CEO. Prior to joining Madera, he was Vice President of Research for Tanabe Research Labs-USA, the US discovery arm of Mitsubishi-Tanabe Pharma. While at Tanabe, he and his team advanced multiple small molecule programs in autoimmunity, inflammation and metabolic disease to the development track. Preceding Tanabe, Dr. Jack was a scientific co-founder and Vice President, Biology at Triad Therapeutics where he oversaw programs in autoimmunity and inflammation including a p38 MAP kinase program for rheumatoid arthritis that was the centerpiece of the Novartis acquisition and that is entering Phase 2 clinical trials. Prior to Triad, Dr. Jack was Vice President for Research and Development at La Jolla Pharmaceutical where he initiated and led programs in autoimmunity and xenotransplantation that included the advancement of several developmental and clinical-stage compounds. Prior to his work in the biopharmaceutical industry, he was a faculty member in the Department of Rheumatology/Immunology at Harvard Medical School where his lab focused on innate immunity and autoimmune disease. He received his A.B. degree from Bates College, his PhD in immunology from the University of Connecticut Health Center and was a post-doctoral fellow in the immunology of parasitic diseases at the International Laboratory for Research in Animal Diseases in Nairobi, Kenya. He is the author of more than 50 papers and several patents.

Optimizing Drug Like Compounds that Increase ApoE Release from Human Astrocytes to Treat Alzheimer's Disease

Rick Jack

Madera Biosciences Inc., San Diego, CA, USA

There is a great need for disease modifying drugs for Alzheimer's disease. Given that beta amyloid (Aβ) accumulation is linked to AD pathogenesis and AD patients have decreased clearance rates of Aβ, we are seeking compounds that increase Aβ clearance from the CNS. Apolipoprotein E (ApoE) mediates clearance of Aβ. Small molecule compounds that increase levels of Aβ are therapeutic in mouse models of AD. We have identified two distinct molecular classes of compounds that increase ApoE production by human astrocytes. The first series, exemplified by MAD7001, is a novel structural class, does not bind to LXR or RXR and is thought to be a novel target. Our SAR studies have improved potency and drug-likeness. Studies are underway to evaluate the lead compounds' *in vivo* performance including pharmacokinetic (PK) and blood-brain barrier (BBB) penetrance.

The second project is exemplified by MAD7001, a novel chemical compound that binds to RXRα and increases both ApoE and ABCA1 production by human astrocytes (EC_{50}=110 nM). Importantly, this molecule does not bind to either LXRα or β, nor does it inhibit any of the 25 protein kinases against which it was tested. MAD7001 is structurally unrelated to any known RXR agonist as well as to MAD7012. Inasmuch as MAD7001 is a neutral molecule that is uncharged at physiological pH, it should have a significantly different distribution *in vivo*, tissue access and plasma protein binding than the typical RXR agonists which are lipophilic carboxylic acids. To our knowledge, this is a unique feature that makes the pursuit of this molecule and its congeners especially promising. Any physicochemical liabilities possessed by acidic RXR agonists such as bexarotene are unlikely to be shared by this class of molecule. Our presentation will focus on preclinical advancements made with the two programs and our plans for moving the compounds to *in vivo* POC and eventually into the clinic.

Nozomi Nishimura, PhD, Cornell University

Dr. Nishimura received her BA in Physics from Harvard University in 1999, where she began working with high-power lasers. She received a PhD in Physics from University of California, San Diego in 2006, where her work in David Kleinfeld's lab shifted to the study of blood flow in the brain using optical methods.

Dr. Nishimura is currently working as a Research Associate in the Schaffer Group at Cornell University where she studies cellular dynamics in rodent models of neurological disease.

Capillary Plugging by Leukocytes Contributes to Blood Flow Reduction in Mouse Models of Alzheimer's Disease

Nozomi Nishimura[1], Gabriel Otte[1], Calvin J. Kersbergen[1], Joan Zhou[1], Jeffrey D. Beverly[1], Iryna Ivasyk[1], Jean Cruz[1], Elizabeth Slack[1], Thom P. Santisakultarm[1], Costantino Iadecola[2] and Chris B. Schaffer[1]

[1]*Cornell Univ., Ithaca, NY, USA*

[2]*Weill Medical College of Cornell Univ., New York, NY, USA*

Alzheimer's disease (AD) is characterized by aggregates of amyloid-beta, which eventually accumulates into dense plaques scattered throughout the brain. Clinical research and experimental work suggest that cerebral blood flow is impaired in AD. In addition, chronically increased inflammation is observed in both AD patients and animal models of AD. We hypothesize that inflammation could contribute to the reductions in blood flow in AD by leukocyte plugging of capillaries.

We used in vivo two-photon excited fluorescence microscopy to examine cortical blood flow in mouse models of AD (B6.Cg-Tg (APPswe,PSEN1dE9)85Dbo/J) implanted with cortical windows. We label the blood vessels by intravenous injection of Texas red-conjugated dextran. To determine whether individual brain microvessels are stalled or flowing, we monitor the movement of non-fluorescent blood cells within the dye-labeled blood plasma. Additionally, methoxy-X04 is used to fluorescently label the amyloid plaques. Intravenous rhodamine-6G and Hoechst enables the discrimination of red blood cells (no label) from nucleated leukocytes and thrombi.

In ~9 month old Alzheimer mice, we found the fraction of capillaries stalled in the cortex to be about four times higher than in same-aged wild-type littermates. In the AD mice, approximately two-thirds of the stalled vessels were plugged by leukocytes. The majority of plugged capillaries in both AD and wild-type animals reperfuse with a ~2 minute half-life, but a small number in AD mice remain for hours. We also find that some capillaries are plugged repeatedly, indicating that these vessels may mark a "hotspot" of inflammation.

This suggests that inflammation in AD could cause significant, chronic leukocyte adhesion and capillary plugging. The resulting reductions in blood flow might contribute to the detrimental cognitive effects of AD.

Cheryl Wellington, PhD, University of British Columbia

Dr. Wellington obtained her PhD in Microbiology at the University of British Columbia in 1991 and did postdoctoral training at Harvard Medical School, the University of Calgary, and the University of British Columbia. She joined the Department of Pathology and Laboratory Medicine at the University of British Columbia in 2000 and was promoted to Professor in 2011. Dr. Wellington's research interests encompass include lipid and lipoprotein metabolism in the brain and how this relates to chronic and acute neurological disorders. Dr. Wellington's group has made key contributions to the understanding of the role of apolipoprotein E (apoE) in Alzheimer's disease. ApoE is the major cholesterol carrier in the brain and the best established genetic risk factor for late-onset Alzheimer's disease. However, the mechanisms by which apoE affects Alzheimer's disease pathogenesis is poorly understood. Dr. Wellington's laboratory has shown that the amount of lipids carried on apoE affects the metabolism of Aβ peptides, which are toxic species that accumulate as amyloid plaques in the brains of patients with Alzheimer's disease and also accumulate in individuals who have suffered traumatic brain injury. Specifically, Dr. Wellington has identified the cholesterol transporter ABCA1 as the physiological transporter of lipids onto brain apoE. Her group has shown that mice deficient in ABCA1 have poorly-lipidated apoE in the brain and develop more amyloid, whereas transgenic mice that over-express ABCA1 have lipid-rich apoE and have virtually no amyloid deposits. Her current research projects are aimed at developing methods to increase apoE lipidation in the brain for application to both Alzheimer's disease and traumatic brain injury.

Preventing Leukocyte Adhesion and Impaired Cerebral Blood Flow as a Treatment Strategy for Alzheimer's Disease

Jianjia Fan[1], Yoko Shimizu[2], Li-wen Tian[3],Yun Jiang Feng[3], Ronald J. Quinn[3], Tom Pfeifer[2], Cheryl Wellington[1]

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Apolipoprotein E (apoE) is the most important genetic risk factor for late-onset Alzheimer's disease (AD) and the majority of AD patients carry the detrimental apoE4 variant. Although the increased genetic risk of apoE4 was discovered in 1993, how apoE contributes to AD has remained unclear. ApoE is the major lipoprotein in the brain and acts to distribute fats among various cells types in the central nervous system. ApoE's role in lipid metabolism is intimately associated with its ability to facilitate the clearance of Ab species that accumulate in the AD brain. Deficiency of the lipid transporter ABCA1 results in poorly-lipidated apoE and increased amyloid in AD mouse models, whereas selective ABCA1 overexpression increases lipid-laden apoE and strongly promotes Aβ clearance. Liver-X-Receptor (LXR) agonists, which induce ABCA1 expression, promote apoE lipidation, facilitate Aβ clearance and restore cognitive function in symptomatic AD mice. However, although effective in preclinical AD models, current LXR agonists are precluded from clinical trials because they will unavoidably lead to fatty liver in humans. With ADDF support, we recently performed a high throughput screen for compounds that increase apoE secretion from CCF-STTG1 astrocytoma cells. Three compounds from the Centre for Drug Research and Development's KD2 library and two compounds from their CCBN library were observed to increase apoE secretion in a dose-dependent manner. Preliminary mechanism of action (MOA) studies evaluating apoE and ABCA1 expression and activity in LXRa/b-deficient cells define three compounds that have partial LXR agonist activity and two compounds that do not. We have also recently identified 11 fractions that exhibit dose-dependent activity on apoE secretion from the NatureBank pre-fractionated natural products library comprising of 102,432 fractions. The 11 active fractions were derived from 11 different Australian marine organisms. Five alkaloids, one new to science, were isolated from a marine sponge *Aplysinella aplysinella*, their activity as an apoE modulator is currently under investigation.

Guojun Bu, PhD, Mayo Clinic

Dr. Bu is a Professor and Consultant in the Department of Neuroscience at Mayo Clinic Jacksonville. Prior to joining Mayo Clinic in late 2010, he was a Professor at Washington University School of Medicine. He is an acknowledged leader in the field of apoE and apoE receptors in Alzheimer's disease. In the early 90s, his research led to the identification of apoE receptor LRP1 as the endocytic receptor for tissue-type plasminogen activator, an enzyme that is clinically used to dissolve blood clots during myocardial infarction and stroke. Dr. Bu has made major contributions to the understanding of LRP1 function in CNS and his seminal work has defined the roles of LRP1 in brain Aβ and apoE metabolism. Dr. Bu's current research includes defining the roles of LRP1 in brain lipid metabolism, synaptic functions and in the pathogenesis of AD. His work also focuses on understanding the mechanisms by which apoE4 acts as a strong risk factor for AD. His review in Nature Reviews Neuroscience in 2009 highlighted critical challenges and opportunities in this research area. Dr. Bu serves as an editorial board member for the Journal of Biological Chemistry and Editor-in-Chief for Molecular Neurodegeneration.

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

Guojun Bu

Mayo Clinic, Jacksonville, FL, USA

Apolipoprotein E (apoE) is a major lipid transporter in the brain. Of the three human apoE isoforms, apoE4 is a strong risk factor for late-onset Alzheimer's disease (AD). ApoE isoforms function differentially in the metabolism and aggregation of amyloid-β (Aβ), a toxic peptide central to the pathogenesis of AD. Additionally, increasing evidence indicates that apoE4 pathogenic pathways in AD are at least partially independent of Aβ. Brain apoE/lipoprotein particles, produced primarily by astrocytes, deliver cholesterol and other lipids to neurons via apoE receptors, which belong to the low-density lipoprotein receptor (LDLR) family. We have demonstrated that brain apoE metabolism is mediated by both LDLR and LDLR-related protein 1 (LRP1). However, our recent work has shown that LRP1 is the predominant neuronal apoE receptor that is critical for apoE/cholesterol transport and synaptic functions. LRP1 and LDLR also facilitate cellular clearance of Aβ. We will present evidence that increasing the expression levels of either apoE or apoE receptors in AD brains will facilitate brain Aβ clearance, enhance cholesterol transport, and protect synapses. To identify chemical compounds that can regulate apoE/apoE receptor expression and benefit synapse and memory, we have recently developed novel ELISA systems for LRP1 and LDLR that allow us to more efficiently and accurately quantify these apoE receptors. Using these ELISAs for apoE and apoE receptors, we have preliminarily screened two compound libraries to identify compounds that can modulate the expression and function of apoE and apoE receptors. We will present preliminary results of our screening efforts. Selected compounds from in vitro screening will be further tested in AD mouse models to address their efficacy in modulating apoE expression, Aβ metabolism, synaptic transmission and memory. Our eventual goal is to conduct clinical trials targeting apoE and apoE receptor pathways in AD therapy.

Thomas Wisniewski, MD, New York University School of Medicine

Dr. Wisniewski is Professor of Neurology, Pathology and Psychiatry at New York Langone School of Medicine. He is Chief of the Division of Aging and Dementia, as well as the Director of the Conformational Disorders Laboratory and the Director of the Memory and Dementia Disorders Center. In addition, he is the Director of the Neuropathology Core of the NYU AD Center, the Director of the Neuropathology Fellowship and Associate Director of Research of the Center of Excellence on Brain Aging. Dr. Wisniewski's laboratory focuses on gaining a better understanding of Alzheimer's and prion related diseases. This work has led to 210 peer-reviewed publications. This work is recognized nationally and internationally. Dr. Wisniewski currently has numerous active grants as a principal investigator, and has had 20 years of continuous funding from NIH. Various studies conducted by Dr. Wisniewski have helped direct our greater understanding of abnormal protein accumulation in the brain towards novel diagnostic and therapeutic interventions.

Development of Peptidomimetic ApoE/Abeta Binding Inhibitors as an Effective and Non-Toxic Therapeutic Approach for AD

Shan Liu, Yanjie Sun, Henrieta Scholtzova and Thomas Wisniewski

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

Inheritance of the apoE4 allele is the strongest genetic risk factor for the most common, late-onset form of AD. However, there is no consensus on how different apoE isotypes contribute to AD pathogenesis. It has been hypothesized that apoE and apoE4 in particular is an amyloid catalyst or "pathological chaperone". Alternatively it has been posited that apoE is an Aβ clearance factor, with apoE4 been worse at this function compared to apoE3 or E2. These views seem fundamentally opposed. The former would indicate that removing apoE would reduce AD pathology, while the latter suggests that increasing brain ApoE levels may be beneficial. We suggest that these seemingly opposing views can be reconciled and that the optimal therapeutic target may be to specifically prevent the interaction of apoE with Ab, rather than altering apoE levels. Such an approach will not have detrimental effects on the many other beneficial roles apoE plays in neurobiology. We show that blocking the Aβ/apoE interaction by Aβ12-28P, a nontoxic blood-brain-barrier permeable and non-fibrillogenic synthetic peptide constitutes a novel therapeutic approach for AD by reducing Aβ parenchymal deposition in APP/PS1 Tg mice and vascular amyloid deposits in TgSwDI mice. In addition have developed effective peptidomimetic antagonists of the Aβ/apoE interaction that are derived from the Aβ12-28P sequence. Peptoid compounds due to their inherent resistance to degradation are known to have more favorable pharmacokinetic properties. Preliminary in vivo data with these peptidomimetic using 3xTg mice with both amyloid and tau pathology will be presented.

Robert W. Mahley, MD, PhD, The J. David Gladstone Institutes

Dr. Robert W. Mahley is president emeritus/founder/senior investigator of The J. David Gladstone Institutes. He is an internationally known expert on heart disease, cholesterol metabolism and, more recently, Alzheimer's disease. His seminal research has defined apolipoprotein (apo) E's critical role in cholesterol homeostasis and atherosclerosis. Dr. Mahley has also made fundamental contributions to understanding the role of apoE in the nervous system, specifically in nerve injury and regeneration and in the remodeling of neurites on neuronal cells. These findings laid the groundwork for the explosion of research linking apoE4, a variant of apoE, to the pathogenesis of Alzheimer's disease and neurodegeneration. More recently, he has focused on therapeutic approaches to converting apoE4 to apoE3, both structurally and functionally, and preventing the generation of apoE4 neurotoxic fragments. Dr. Mahley is also a professor of pathology and medicine at the University of California, San Francisco. He is a member of the National Academy of Sciences, the Institute of Medicine, and the American Academy of Arts & Sciences. He recently received the 2010 Builders of Science Award from Research!America for his leadership as Gladstone's founding director and president, guiding its growth to become one of the world's foremost independent research institutes, the 2011 American Heart Association's Distinguished Scientist Award, and the 24th Annual Robert J. and Claire Pasarow Foundation Award in Cardiovascular Research (2012).

Identification of Small Molecules that Can Prevent Mitochondrial Dysfunction *Associated with* the Generation of Apolipoprotein E Fragments in Neurons

Robert W. Mahley

Gladstone Institute of Neurological Disease & University of California, San Francisco, San Francisco, CA, USA

Apolipoprotein (apo) E4, the major gene and risk factor for Alzheimer's disease, assumes a pathological conformation—intramolecular domain interaction. ApoE structure correctors that abolish domain interaction were identified by fluorescence resonance energy transfer (FRET) assay. A series of small-molecule structure correctors have been identified that exhibit the ability to block apoE4 domain interaction at low nM concentrations. ApoE4 domain interaction is known to mediate the apoE4-specific effects of decreasing mitochondrial cytochrome c oxidase subunit I (~40%), reducing mitochondrial motility (~35%), and significantly inhibiting neurite outgrowth. Small-molecule structure correctors restored these cellular functions to levels equivalent to those of apoE3. Results from the functional assays correlated well with the abilities of small molecules to block apoE4 domain interaction.

Conclusion: We have established that structure correctors are capable of disrupting domain interaction of newly synthesized apoE4 in the secretory pathway and reversing the apoE4-specific detrimental effects on neuronal cells. These results serve as a proof-of-concept that pharmacological intervention by structural correctors can negate the detrimental effects of apoE4 and suggests a potential therapeutic approach.

References: Mahley *et al., Proc. Natl. Acad. Sci. USA* 103:5644–5651, 2006; Chen *et al., J. Biol. Chem.* 287:5253–5266, 2012.

IV. Biomarkers to Accelerate Clinical Development

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

Effects of Brain Beta-Amyloid on Postoperative Cognition
Marek Brzezinski, MD, PhD, University of California, San Francisco

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

Imaging Agents for Diagnosis of Tauopathic Neurodegenerative Diseases
Jeff Kuret, PhD, Ohio State University

[18F]-THK523, a Novel In Vivo Tau Imaging Agent
Victor L. Villemagne, MD, Austin Health

High Resolution Quantitative Magnetization Transfer Imaging in Entorhinal Cortex
Ying Wu, MD, NorthShore University Health System Research Institute

TDP-43 and Tau as Cerebrospinal Fluid Biomarkers to Discriminate Frontotemporal Dementia Subtypes
Marcel M. Verbeek, PhD, Radboud University Medical Center, Nijmegen

Marek Brzezinski, MD, PhD, University of California, San Francisco

Marek Brzezinski, MD, PhD is an Associate Professor in the Department of Anesthesia and Perioperative Care at University of California-San Francisco. He received his MD and PhD degrees from the Westfaelische Wilhelms-University in Muenster, Germany. He completed his anesthesia residency at University of Chicago. Subsequently, he went to Massachusetts General Hospital and Duke University where he completed fellowship training in critical care medicine and in cardiothoracic anesthesia, respectively. His research examines the effects of surgical stress on cognition and neuropsychiatric symptoms, with particular focus on the interaction between neurocognitive function and post-traumatic stress disorder (PTSD). His interest focuses on identifying preoperative neuroimaging biomarkers that best predict postoperative cognitive decline. In addition, Dr. Brzezinski is a nationally accomplished medical educator, member of the prestigious Haile T. Debas Academy of Medical Educators at UCSF, who won multiple national and international awards for his scholarly work.

Effects of Brain Beta-Amyloid on Postoperative Cognition

Marek Brzezinski

University of California, San Francisco, San Francisco, CA, USA

Postoperative cognitive decline, encompassing both the early onset of postoperative delirium and the longer-lasting postoperative cognitive dysfunction (POCD) affects up to 50% of non-cardiac surgical patients ≥ 60 years of age and adversely affects short- and long-term outcomes including mortality rates. This is a major health issue as this age group accounts for almost half of all surgeries performed in the Unites States. Therefore, it is critical to develop novel diagnostic tools to identify susceptible patients at risk for developing cognitive decline after surgery. Preexistent Alzheimer's disease (AD) pathology may increase the risk for the development of cognitive decline postoperatively. The extent of the neuropathology of these early stages of AD can now be detected non-invasively with amyloid β (Aβ) specific PET ligands. This talk will review the current state of research on the effects of brain beta-amyloid on postoperative cognition.

James P. Bennett, Jr., MD, PhD, Virginia Commonwealth University

Dr. Bennett is a native of St. Petersburg, Florida and received his BS in Chemistry with Honors from the University of Florida in 1970. He then attended Johns Hopkins University School of Medicine and received his MD degree in 1974 and his PhD in Pharmacology in 1977. While a graduate student he worked under Dr. Solomon Snyder and remained in Dr. Snyder's laboratory for a research fellowship from 1976-78. He then completed two years of Internal Medicine residency and came to the University of Virginia in 1980 for his Neurology residency that he finished in 1983. From 1982-83 he was Chief Resident in Neurology. In 1983 he joined the faculty in the Neurology Department as Assistant Professor. In 1990 he was promoted to Associate Professor and he received tenure in 1992. In 1997 he was promoted to Professor of Neurology and Psychiatric Research. In 2004 he was awarded the Arthur and Margaret Ebbert Chair in Medical Science. In 2009 he moved to Virginia Commonwealth University and became Bemiss Professor, Chair of Neurology, and founding Director of the VCU Parkinson's Disease Research and Treatment Center. Dr. Bennett has held numerous research grants from the NIH and private foundations. He has been Principal Investigator on three individual investigator (R01) grants and has been Program Director on two NIH Program Projects (NINDS and NIA). He was Director of the Udall Parkinson's Disease Research Center at University of Virginia that was funded for 10 years. He has authored 133 peer-reviewed scientific papers and several book chapters. His clinical specialty is movement disorders, particularly Parkinson's disease. His research interest is in the area of the molecular biology of neurodegenerative brain diseases and the involvement of mitochondria in this process.

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

James P. Bennett, Jr.

Virginia Commonwealth University, Richmond, VA, USA

Our group is pursuing our own version of the "mitochondrial cascade hypothesis of Alzheimer's disease" (Swerdlow RH, Burns JM, Khan SM. J Alzheimer's Dis. 2010;20 Suppl 2:S265-79). In our formulation, impaired mitochondrial bioenergetics is an early event in vulnerable AD brain regions that lead to reduced energy production and increased oxidative stress. This problem is compounded by down-regulation of mitochondrial biogenesis signaling, a paradoxical situation for high-energy brain. The net result is impaired mitochondrial energy production that increases vulnerability of neurons to death signals.

R(+) pramipexole is a benzothiazole neuroprotectant that is orally active, tolerated in high doses and accumulates as a lipophilic cation into mitochondrial matrix where it functions as a free radical scavenger of commonly occurring free radicals and oxidants. Under the auspices of a physician-sponsor IND, R(+)PPX was developed, starting in 2004, as a neuroprotectant for patients suffering from ALS. This use of R(+)PPX was licensed to Knopp Biosciences in 2006 and subsequently to Biogen-Idec in 2009. Biogen-Idec is currently sponsoring Phase III testing of R(+)PPX therapy in ALS.

R(+)PPX, which possesses minimal dopamine receptor activity, is also potentially useful as disease-altering treatment in Alzheimer's disease to reduce oxidative stress and preserve mitochondrial function. The current ADDF-sponsored study involves administration of R(+)PPX in escalating doses up to 300 mg/day to early AD subjects who are followed clinically and with pre/post treatment LP's for biomarker analyses and 18F-2DG PET scans to assay cerebral metabolism. The clinical trial is taking place at Kansas University Medical Center ADRC, Jeff Burns, MD, PI. Current enrollment status, drug tolerability and biomarker responses will be presented and discussed.

Jeff Kuret, PhD, Ohio State University

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

Imaging Agents for Diagnosis of Tauopathic Neurodegenerative Diseases

Jeff Kuret

Ohio State University, Columbus, OH, USA

Current whole-brain imaging methods for dementia target the aggregated forms of the β-amyloid (Aβ) peptide that accumulate in senile plaques. Development of selective radiotracers for tau-bearing neurofibrillary lesions could complement the established Aβ imaging signature in several ways. First, neurofibrillary lesions appear at certain sites of predilection decades before the onset of dementia, potentially providing the means to detect disease at very early stages. Second, unlike Aβ aggregates, tau aggregate load correlates with neurodegeneration and cognitive decline in AD, providing a potential surrogate marker for disease. Because of the well-established relationship between disease progression and spatial distribution of neurofibrillary pathology, tau-based imaging could help establish Braak stage in living patients. Finally, tau-based imaging agents also may aid the diagnosis of dementing illnesses that lack Aβ lesions and that are difficult to distinguish based solely on clinical presentation, including chronic traumatic encephalopathy and certain forms of frontotemporal lobar degeneration. Here I will summarize our progress in developing tau-based imaging agents. First, I will introduce a target product profile built on the basis of nonlinear pharmacokinetic modeling. Second, I will describe the key barriers to meeting target properties, and our strategy for overcoming them. Finally, I will summarize the status of current preclinical lead optimization efforts.

Victor L. Villemagne, MD, Austin Health & The Mental Health Research Institute

After graduating *Cum Laude* in Medicine in 1983, Dr. Villemagne continued his post-graduate studies at the Division of Nuclear Medicine at the Johns Hopkins Medical Institutions. Dr. Villemagne subsequently furthered his functional neuroimaging research at the National Institute on Drug Abuse, NIH, and at the University of Pittsburgh, before joining the Melbourne Neurodegeneration team in 2003. He has over a 100 publications in international peer-reviewed journals on PET research, particularly in the field of neuroscience and neuroreceptor studies. He has been invited to chair and present at national and international meetings in the area of biomarkers for Alzheimer's disease and neurodegeneration. In 2001, he received the Foerderer Fund for Excellence Award from The Children's Hospital of Philadelphia in the USA, the ANSTO Neuroscience Nuclear Medicine Award, and in 2007 the JAAME Fellowship from the Ministry of Health and Labor in Japan. Currently, Dr. Villemagne is CI in several NHMRC project grants, a NEDO grant from Japan and an ADDF grant from the USA involving Ab and tau imaging and the characterization of new blood borne Alzheimer's disease biomarkers.

[18F]-THK523, a Novel in Vivo Tau Imaging Agent

Victor L. Villemagne,[1,2]

1. Centre for PET, Austin Health, Melbourne, Australia
2. The Mental Health Research Institute, Melbourne, Australia

Definitive diagnosis of tauopathies such as Alzheimer's disease (AD), some variants of frontotemporal lobe degeneration, progressive supranuclear palsy and corticobasal degeneration, is still reliant upon post-mortem examination of the human brain. Furthermore, these diseases are often difficult to differentiate clinically due to overlapping phenotypes, especially at early stages of their development. In vivo imaging with PET will allow new insights into tau deposition in the human brain, facilitating research into causes, diagnosis and treatment of taupathies, as is now available for Aβ. We have characterized 18F-THK523, a novel tau imaging ligand developed at Tohoku University in Sendai, Japan, assessing its selectivity and specificity for tau pathology both in vitro and in vivo. In vitro binding studies demonstrated that 18F-THK523 binds with higher affinity to a greater number of binding sites on recombinant tau compared with Aβ1-42 fibrils. Autoradiographic and histofluorescence analysis of human AD hippocampal brain sections, demonstrated that THK523 co-localized with immunoreactive tau pathology, but failed to highlight Aβ plaques. In small animal PET studies, there was higher brain retention of 18F-THK523 in tau transgenic (rTg4510) mice compared with their wild-type littermates or APP/PS1 mice. The preclinical examination of THK523, with its high affinity and selectivity for tau pathology both in vitro and in vivo, indicated that 18F-THK523 fulfilled ligand criteria for human PET studies. Initial human PET studies comparing 18F-THK523 and 11C-PiB have shown that 18F-THK523 does not bind to Aβ in AD. In contrast with the 11C-PiB PET scans, there were no distinctive visual features in the 18F-THK523 PET scans differentiating the groups being studied. Despite this, significantly higher cortical retention in the parietal, frontal and hippocampus, albeit much lower than the observed with 11C-PiB, was detected in AD patients when compared to healthy controls and patients diagnosed with Semantic Dementia. Further studies are needed to confirm these initial findings.

Ying Wu, MD, NorthShore University Health System Research Institute

Ying Wu is a biomedical scientist, trained radiologist, and imaging laboratory leader within a multi-billion dollar healthcare and research organization, directing all aspects of Image Processing Laboratory operations while simultaneously performing scientific research into the use of quantitative MRI in early detection of neurological disease. Dr. Wu designs and develops clinical research studies, forges collaborative relationships with partner research facilities and clinicians, defines IRB- and FDA-compliant clinical research protocols, recruits participants, and creates computer software for automated image processing and analysis. She manages IT infrastructure procurement, installation, configuration, and administration spanning hardware, software, and networking technology. She provides direct leadership across the lab to all scientific, technological, and operational staff.

Dr. Wu is currently a clinical research scientist at NorthShore University Health System, and research associate professor (pending) at the University of Chicago. From 1999-2003, she was a research fellow at the Center for Neurological Imaging at the Brigham and Woman's Hospital at Harvard Medical School, developing automated computer image processing algorithm. She is the author or co-author of more than 30 scientific and clinical publications, has proven clinical research acumen and success in obtaining grant funding. She is the clinical collaborative program leader at her institution conducting Neuroimaging initiative developing Bio-imaging markers in Alzheimer's disease and healthy aging.

High Resolution Quantitative Magnetization Transfer Imaging in Entorhinal Cortex

Ying Wu

NorthShore University Health System Research Institute, Evanston, IL, USA

A significant obstacle in developing anti-Alzheimer's disease (AD) drugs is inability to accurately diagnose the disease early or to monitor brain changes noninvasively. There is tremendous need for developing reliable, noninvasive imaging markers to detect early changes and to monitor disease progression in living brain to prompt therapeutic intervention and slow disease. We have developed high resolution MR technique to facilitate accurate quantification in small brain anatomical structures crucial in early AD detection. We combined multiple novel MR imaging modalities to examine different levels of microscopic brain tissue integrity and brain function to improve diagnostic sensitivity. With the large amount of data generated the current manual measurement methods are insufficient and inconsistent. Thus, we created atlas based automated post processing toolbox for reliable and consistent measurement across time and space. We are currently recruiting groups of clinically well-defined AD and normal aging to identify MR markers. Our future goals are to assist clinical diagnosis of AD and to improve data mining in larger scale clinical and pharmaceutical trials.

Marcel M. Verbeek, PhD, Radboud University Medical Center, Nijmegen

Dr. Marcel M. Verbeek is head of the National Reference Centre for CSF analysis in the Radboud University Medical Center, Nijmegen, the Netherlands. This Centre offers dedicated and specialized neurochemical analyses in body fluids (primarily cerebrospinal fluid) to all hospital in the Netherlands and abroad and runs national QC programs for CSF analysis. The research interest of Marcel M. Verbeek is primarily focused on neurodegenerative disorders, in particular dementias and movement disorders. One focus is on the development and clinical validation of novel neurochemical biomarkers for neurodegenerative disorders (Alzheimer's disease and related disorders; Parkinson's disease and related disorders). Another focus is the study of aggregating proteins (amyloid β, α-synuclein) and their biological effects (clearance, cellular toxicity, interaction with chaperones, inflammation) with regard to the pathofysiology of Alzheimer's and Parkinson's disease. Dr. Verbeek has approximately 150 publications in peer-reviewed journals. He has acquired grants from (amongst others): The Alzheimer's Association (US), The Netherlands Brain Foundation, Center for Translational Molecular Medicine, Internationale Stichting Alzheimer Onderzoek, Netherlands Organization for Scientific Research.

TDP-43 and Tau as Cerebrospinal Fluid Biomarkers to Discriminate Frontotemporal Dementia Subtypes

M.M. Verbeek, A. Versleijen, M. Beenes, B. Küsters, H.B. Kuiperij

Radboud University Medical Centre, Nijmegen, the Netherlands
Donders Institute for Brain, Cognition and Behaviour, Alzheimer Centre Nijmegen, Nijmegen, the Netherlands

Background: Frontotemporal dementia (FTD) is the second most common dementia next to Alzheimer's disease. Almost half of the FTD cases are recognized by tau-positive inclusions, referred to as FTD-tau. Familial FTD-tau cases are linked to mutations in the gene coding for microtubule associated protein tau (*MAPT*). The remaining patients are mostly characterized neuropathologically by inclusions containing the (phosphorylated) protein TDP-43, referred to as FTD-TDP. TDP-43-positive inclusions are also found in amyotrophic lateral sclerosis (ALS) and Alzheimer's Disease (AD). Due to clinical heterogeneity and overlap with other neurodegenerative diseases, a reliable clinical diagnosis of FTD is difficult.
We **hypothesize** that cerebrospinal fluid (CSF) levels of total tau protein (t-tau), phosphorylated tau protein (p-tau), and TDP-43 protein (t-TDP-43 and p-TDP43, respectively) and p-TDP-43 reflect the underlying FTD pathogenesis and, as a consequence, provide a tool to diagnose the various FTD subtypes during life.
Aims: Our goal is to investigate whether a correlation exists between the neuropathological / genetic phenotype of FTD and the neurochemical composition of CSF.
Methods: We developed sensitive and robust assays to quantify t-TDP-43 and p-TDP-43 in body fluids and validated the use of these assays in CSF samples of patients with FTD-tau, FTD-TDP, AD and of controls. Commercial assays were used to quantify t-tau and p-tau in CSF.
Results: Assays to quantify either t-TDP-43 or p-TDP-43 were demonstrated to be specific and reliable. P-TDP-43 can be reliably measured in serum and ventricular CSF, but not in lumbar CSF. T-TDP-43 can be reliably measured in serum and ventricular CSF. Strikingly, t-TDP-43, p-TDP-43 and t-tau concentrations were lower in ventricular CSF of FTD-tau, FTD-TDP and AD than in controls. Importantly, we demonstrated that a combination of t-tau and t-TDP-43 in ventricular CSF can differentiate FTD-tau and FTD-TDP subgroups (AUC=0.79).
Conclusions: Our results suggest that the combined quantification in CSF of t-tau and t-TDP-43 may serve as biomarkers to distinguish FTD subtypes. These studies will be extended to the analysis of other body fluids (lumbar CSF, serum) of FTD patients and related disorders, but also to body fluids of other TDP-proteinopathies such as ALS.

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