Alzheimer's Drug Discovery Foundation

20TH
INTERNATIONAL
CONFERENCE
ON
ALZHEIMER'S
DRUG DISCOVERY

Jersey City, NJ ⬡ *September 16-17, 2019*
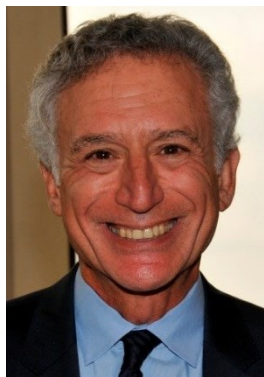
PROGRAM and ABSTRACTS

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WELCOME

On behalf of the Alzheimer's Drug Discovery Foundation (ADDF), I am pleased to welcome you to our *20th International Conference on Alzheimer's Drug Discovery.*

The 20th year of this meeting is an important landmark for ADDF. From the earliest meetings to today, the changes in agenda topics reflect progress in the field over the past two decades. The earliest meetings featured a program primarily focused on early stage preclinical drug development. Our 20th meeting features a plenary lecture on precision medicine, showcases results from completed clinical trials, highlights new biomarker modalities such as blood and eye tests, and expands to learn from other neurodegenerative diseases.

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

We are deeply grateful to Merck whose continued support makes this meeting possible. We would also like to thank our exhibitors: InterVivo Solutions, Charles River, MagQu, Recruitment Partners, Konica Minolta and Alzheimer's Clinical Trials Consortium. Our sincere appreciation also extends to all our speakers for the hard work they do to accelerate drug discovery and development for Alzheimer's disease and related dementias.

Engaging the next generation of research scientists in this field is more important than ever. This year, we have awarded 15 scholarships to young researchers in the field. Three of them will present in the Data Blitz session while the rest will showcase their work within the poster sessions which we invite you to attend.

To help us plan an even better conference in 2020, we kindly ask you to complete the meeting survey to provide us with feedback and suggestions.

Welcome, once again, to the 20th International Conference on Alzheimer's Drug Discovery!

Best Regards,

Howard

Howard Fillit, MD
Founding 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 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 **$130 million to fund over 600 programs for Alzheimer's and related dementias in** academic centers and biotechnology companies in **19 countries**.

- In 2018, the ADDF committed $20 million to support preclinical, clinical, and biomarker development programs. 100% of funds raised went directly to drug research and related scientific programs, thanks to the generosity of our founders who cover all administrative and operational expenses.

- 2018 also marked the launch of the ADDF's Diagnostics Accelerator initiative, a $50 million fund dedicated to the development of accessible and affordable biomarkers for Alzheimer's and related dementias. The three-year initiative brings together funding from a coalition of philanthropists including ADDF Co-Founder Leonard Lauder, Bill Gates and Jeff and MacKenzie Bezos, among others.

OUR CONFERENCES

The Alzheimer's Drug Discovery Foundation organizes two annual 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.

In addition to the *International Conference for Alzheimer's Drug Discovery* here in Jersey City, we organize the *Drug Discovery for Neurodegeneration* conference, held annually in the spring, which is designed to educate scientists on the process of translating basic neuroscience research into innovative therapies.
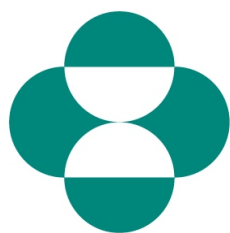
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2019 ADDF YOUNG INVESTIGATOR SCHOLARSHIPS

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 or podium presentations. Please visit their poster presentations during the breaks, lunch and networking reception.

Three Young Investigator Scholars have been selected to present their work in a 10-minute podium presentation on Monday, September 16, at 4:35 pm. The recipients of this opportunity are:

Nicole Kasica, PhD (cand.), *Wake Forest University, Winston-Salem, NC, United States*

Christina Tognoni, PhD, *Boston University/VA Boston Healthcare System, Boston, MA, United States*

Shanshan Wang, MD, PhD, *USCD, San Diego, CA, United States*

The 2019 Young Investigator Scholars are:

Jessica Dennison, PhD (cand.), *University of Miami Miller School of Medicine, Miami, FL, United States*

Ruben Gomez-Gutierrez, PhD (cand.), *University of Texas Health Science Center at Houston, Houston, TX, United States*

Manoj Govindarajulu, PhD (cand.), *Harrison School of Pharmacy, Auburn, AL, United States*

Krupal Jethava, MS, PhD, *Purdue University, West Lafayette, IN, United States*

Rachel Knopp, *University of Illinois at Chicago, Chicago, IL, United States*

Goodwell Nzou, PhD, *University of Pennsylvania, Philadelphia, PA, United States*

Sindhu Ramesh, PhD (cand.), *Harrison School of Pharmacy, Auburn, AL, United States*

Natalie Ricciardi, BS, *University of Miami, Miami, FL, United States*

Chinedu Udeh-Momoh, MS, PhD, *Imperial College London, United Kingdom*

Zhiyu Wang, PhD (cand.), *University of Toronto, Toronto, ON, Canada*

Yulong Xu, PhD, *Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States*

PROGRAM

Monday, September 16	
8:00am–5:30pm	Registration
8:00–9:00am	Continental Breakfast
9:00–9:20	**Welcome & Introductory Notes** Howard Fillit, MD—*Alzheimer's Drug Discovery Foundation*
9:20–9:50	**KEYNOTE: Extracellular Vesicle Biomarkers Revolutionize Preclinical Diagnosis of AD and Assessment of Treatment Responses in Clinical Trials** Dimitrios Kapogiannis, MD—*National Institutes of Health*
9:50-10:00	Q&A
Session I: SMALL MOLECULE APPROACHES FOR ALZHEIMER'S DISEASE Chair: Lauren Friedman, PhD—*Alzheimer's Drug Discovery Foundation*	
10:00–10:05	**Session Overview:** Lauren Friedman, PhD—*Alzheimer's Drug Discovery Foundation*
10:05–10:25	**Q134R: Novel Small Chemical Compound with NFAT Inhibitory Properties Ameliorates Synaptic Deficits in a Mouse Model of Alzheimer's Disease** Christopher Norris, PhD—*University of Kentucky*
10:25–10:35	**Q&A**
10:35–10:55	**Inhibiting Ryanodine Receptors, an ER Calcium Channel, to Prevent Synaptic Pathology and Protein Mishandling** Grace (Beth) Stutzmann, PhD—*Chicago Medical School/NeuroLucent, Inc*
10:55–11:05	**Q&A**
11:05–11:35	**EXHIBITOR SESSION BREAK**
11:35–11:55	**Design and Exploration of NLRP3 Inhibitors for Neurodegenerative Disorders** Shijun Zhang, PhD—*Virginia Commonwealth University*
11:55am–12:05pm	**Q&A**
12:05–12:25	**Pharmacological Inhibition of EP2 Receptors Suppress Neuroinflammation in the Female 5xFAD Mice, but not in the Male 5xFAD Mice** Thota Ganesh, PhD—*Emory University*
12:25–12:35	**Q&A**
12:35–1:05	**POSTER SESSION**
1:05–2:00	**LUNCH**
Session II: NOVEL APPROACHES FOR FRONTOTEMPORAL DEMENTIA Chair: Meriel Owen, PhD—*Alzheimer's Drug Discovery Foundation*	
2:00–2:05	**Session Overview:** Meriel Owen, PhD—*Alzheimer's Drug Discovery Foundation*
2:05–2:25	**TDP-43 Proteinopathies: Challenges and Opportunities for a Pathology-Specific Biofluid Test** Mari DeMarco, PhD—*University of British Columbia*
2:25–2:35	**Q&A**
2:35–2:55	**Human Microglial and Neuronal Models of Frontotemporal Dementia and Strategies to Rescue Progranulin Haploinsufficiency** Steven Finkbeiner, MD, PhD—*Gladstone Institutes/University of California, San Francisco*
2:55–3:05	**Q&A**
3:05–3:25	**Blood Biomarker Monitoring in Frontotemporal Lobar Degeneration: the Neurofilament Light Surveillance Project (NSP)** Rodney Pearlman, PhD—*The Bluefield Project to Cure FTD*
3:25–3:35	**Q&A**
3:35–3:55	**Non-Invasive Brain Stimulation to Restore Cortical Connectivity in FTD** Alberto Benussi, MD—*University of Brescia*
3:55–4:05	**Q&A**
4:05–4:35	**EXHIBITOR SESSION BREAK**

4:35–5:20	**EMERGING CONCEPTS: DATA BLITZ** Chair: Meriel Owen, PhD—*Alzheimer's Drug Discovery Foundation* **Neuron-targeted Caveolin-1 Preserves Hippocampal Neuroplasticity and Memory in AD Mice** Young Investigator #1: Shanshan Wang, MD, PhD—*University of California, San Diego* **Treatment with AUY954, a Selective Sphingosine-1-Phosphate Receptor 1 Agonist, Reduces Early Development of AI Pathology and Neuroinflammation in a Mouse Model of Alzheimer's Disease** Young Investigator #2: Christina Tognoni, PhD—*Boston University/VA Boston Healthcare System* **Memory Impairments and Synaptic Failure in Tg19959 AD Model Mice Are Alleviated by Eef2k Inhibitor A-484954** Young Investigator #3: Nicole Kasica, PhD(cand.)—*Wake Forest University*
5:20–5:30	**Closing Remarks and Announcement of Young Investigator Scholarships** Meriel Owen, PhD—*Alzheimer's Drug Discovery Foundation*
5:30–7:00	**NETWORKING RECEPTION**

Tuesday, September 17

7:30-8:20	Continental Breakfast
8:20–8:50	**SPECIAL SESSION: NIA Alzheimer's and Related Dementias Translational Research Funding Opportunities** Zane Martin, PhD—*National Institute on Aging*
8:50–9:20	**KEYNOTE: The Use of Platform Trials in CNS Disorders** Sabrina Paganoni, MD, PhD—*Massachusetts General Hospital/Harvard University*
9:20-9:30	**Q&A**

Session III: CLINICAL TRIALS IN ALZHEIMER'S DISEASE
Chair: Alessio Travaglia, PhD—*Alzheimer's Drug Discovery Foundation*

9:30–9:35	**Session Overview:** Alessio Travaglia, PhD—*Alzheimer's Drug Discovery Foundation*
9:35–9:55	**Rasagiline Rescue (R2): A Double-Blind Placebo Controlled Trial for Mild to Moderate Alzheimer's Disease** Jeffrey Cummings, MD, ScD—*Cleveland Clinic*
9:55–10:05	**Q&A**
10:05–10:25	**Clinical Biomarker Evidence for Target Engagement, Reduction of Synaptic Damage and Disease Modification in Alzheimer's Patients Treated with CT1812 (Elayta™)** Susan Catalano, PhD—*Cognition Therapeutics*
10:25–10:35	**Q&A**
10:35–11:05	**EXHIBITOR SESSION BREAK**
11:05–11:25	**Vafidemstat: The First Epigenetic Approach in Alzheimer's Disease** Roger Bullock, MBBS—*Oryzon*
11:25–11:35	**Q&A**
11:35–11:55	**Vascular Approaches for Alzheimer's Treatment** Ihab Hajjar, MD—*Emory Health Care*
11:55am–12:05pm	**Q&A**
12:05–12:35	**POSTER SESSION**
12:35–1:15	**LUNCH**

Session IV: NOVEL BIOMARKER APPROACHES
Chair: Nicole Bjorklund, PhD—*Alzheimer's Drug Discovery Foundation*

1:15–1:20	**Session Overview:** Nicole Bjorklund, PhD—*Alzheimer's Drug Discovery Foundation*
1:20 –1:40	**FDG PET, Tau PET, and MR Imaging Biomarkers in Alzheimer's Disease Therapeutic Trials** Dawn Matthews, MS—*ADMdx*
1:40–1:50	**Q&A**
1:50–2:10	**Resilience Biomarker NPTX2 and AD Progression** Paul Worley, MD—*Johns Hopkins University*
2:10–2:20	**Q&A**
2:20–2:40	**The Utility of cFLIP and MCL 1 and their Regulatory MicroRNAs as Novel Biomarkers of Alzheimer's Disease** Esmerina Tili, PhD—*OSU/Gnome Diagnostics, LLC*
2:40–2:50	**Q&A**
2:50-3:10	**Ocular Approaches for Alzheimer's Diagnosis** Swati More, PhD—*University of Minnesota*
3:10-3:20	**Q&A**
3:20-3:30pm	**Closing Remarks** Howard Fillit, MD—*Alzheimer's Drug Discovery Foundation*

BIOS AND ABSTRACTS

CONFERENCE CHAIR
Howard Fillit, MD—Alzheimer's Drug Discovery Foundation
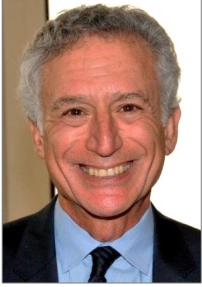
Howard Fillit, MD, a geriatrician, neuroscientist and a leading expert in Alzheimer's disease, is the founding Executive Director of the Alzheimer's Drug Discovery Foundation (ADDF). The ADDF's mission is to accelerate the discovery and development of drugs to prevent, treat and cure Alzheimer's disease, related dementias and cognitive aging. Dr. Fillit has had a distinguished academic medicine 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 is a co-author of more than 300 scientific and clinical publications and is the senior editor of the leading international Textbook of Geriatric Medicine and Gerontology.

Previously, Dr. Fillit was the Corporate Medical Director for Medicare at New York Life, responsible for over 125,000 Medicare managed care members in five regional markets. Dr. Fillit has received several awards and honors including the *Rita Hayworth Award for Lifetime Achievement*. He also serves as a consultant to pharmaceutical and biotechnology companies, health care organizations and philanthropies. Throughout his career, he has maintained a limited private practice in consultative geriatric medicine with a focus on Alzheimer's disease and related dementias.

KEYNOTE SPEAKER

Dimitrios Kapogiannis, MD—National Institutes of Health

Dimitrios Kapogiannis, MD, is a Clinical Investigator at the Laboratory of Clinical Investigations at the National Institute on Aging, NIH, and adjunct Associate Professor at the Department of Neurology at Johns Hopkins Medicine. Dr. Kapogiannis earned his Medical Degree from the National University of Athens, Greece, and completed his Neurology residency training at Harvard University/Massachusetts General/Brigham and Women's Hospitals, followed by a clinical fellowship at the National Institute of Neurological Disorders and Stroke. Dr. Kapogiannis is ABPN-certified in Neurology and UCNS-certified in Behavioral Neurology.

Dr. Kapogiannis leads a laboratory at the National Institute on Aging conducting translational and clinical studies on various neurodegenerative diseases with a primary focus on discovering novel biomarkers for diagnosis and preclinical prediction of Alzheimer's disease. Dr. Kapogiannis has been a pioneer in deriving Extracellular Vesicles enriched for neuronal and astrocytic origin from peripheral blood and using them as a source of biomarkers for Alzheimer's disease.

Extracellular Vesicle Biomarkers Revolutionize Preclinical Diagnosis of AD and Assessment of Treatment Responses in Clinical Trials

Dimitrios Kapogiannis

National Institutes of Health

Alzheimer's disease (AD) and other neurodegenerative diseases have long preclinical phases with active and progressively irreversible pathology. Therefore, biomarkers are essential for identifying patients early in the course of these diseases, when they may benefit the most from disease-modifying interventions. A limitation of biomarkers measured in the soluble phase of blood is their tenuous link to brain pathology. A new approach to biomarker discovery that addresses this limitation is deriving extracellular vesicles (EVs) enriched for neuronal and astrocytic origin from peripheral blood. EVs are membranous particles (smaller exosomes and larger microvesicles) that are shed by all cells and found in all biofluids. Neuronal and astrocytic EVs have been implicated in the pathogenesis of several neurodegenerative diseases and may play a role in the spread of tau and Aβ pathologies in AD. Given their origin, neuronal and astrocytic enriched EVs harvested from blood can be used to interrogate brain pathologic processes previously inaccessible in vivo. In a series of case control studies based on circulating EV subpopulations, we identified candidate protein biomarkers for AD, including phosphorylated tau, Aβ42, phosphorylated insulin receptor substrate-1 (IRS1), and complement. Recently, we completed a large (~ 900 sample) validation study of neuronal EV biomarkers, leveraging preclinical longitudinal samples from Baltimore Longitudinal Study of Aging participants who developed AD and demonstrating high accuracy and specificity for predictive discrimination about 4 years before symptom onset. Moreover, individual biomarkers were associated with cognitive performance. Similar findings are being generated and will be presented from other large cohorts, including the Wisconsin Registry for Alzheimer's Prevention (WRAP) and the Atherosclerotic Risk in Communities (ARIC) studies, collectively highlighting the potential of EV biomarkers in delivering preclinical diagnosis for AD. In addition, results from studies demonstrating EV biomarker responses to experimental interventions (e.g. with intranasal insulin) will be presented. EV-based biomarkers are a valuable new tool that may enable researchers to test hypotheses in proof of concept studies with carefully selected participants at the preclinical phase, spearheading therapeutic discovery in AD.

SESSION I: SMALL MOLECULE APPROACHES FOR ALZHEIMER'S DISEASE

Chair: Lauren Friedman, PhD—Alzheimer's Drug Discovery Foundation

Lauren Friedman, PhD, is the Director of Scientific Affairs at ADDF. She oversees ADDF's drug discovery, clinical trial, biomarker and key partnership initiatives.

Dr. Friedman completed her postdoctoral training at Columbia University, where she studied modulators of autophagy in Alzheimer's disease. She earned a doctorate in neuroscience at the Icahn School of Medicine at Mount Sinai, where she focused on molecular mechanisms underlying the development and degeneration of brain circuits involved in autism and Parkinson's disease. She received a bachelor's degree in biopsychology from Tufts University. Dr. Friedman has authored numerous peer-reviewed publications and is a member of the Society for Neuroscience, New York Academy of Sciences and the Association for Women in Science.

Q134R: Novel Small Chemical Compound with NFAT Inhibitory Properties Ameliorates Synaptic Deficits in a Mouse Model of Alzheimer's Disease
Christopher Norris, PhD—University of Kentucky

Inhibiting Ryanodine Receptors, an ER Calcium Channel to Prevent Synaptic Pathology and Protein Mishandling
Grace (Beth) Stutzmann, PhD— Rosalind Franklin University of Medicine and Science/NeuroLucent, Inc

Design and Exploration of NLRP3 Inhibitors for Neurodegenerative Disorders
Shijun Zhang, PhD—Virginia Commonwealth University

Pharmacological Inhibition of EP2 Receptors Suppress Neuroinflammation in the Female 5xFAD Mice, but not in the Male 5xFAD Mice
Thota Ganesh, PhD—Emory University

Christopher Norris, PhD—University of Kentucky

Christopher Norris, PhD, Professor and Associate Director of Research and Faculty Advancement at the University of Kentucky Sanders-Brown Center on Aging (SBCoA).

Chris Norris received his PhD in Neuroscience from the University of Virginia in 1998, working in the lab of Dr. Tom Foster. His dissertation research showed that hippocampal synapses in aged rats were more susceptible to activity-dependent depression arising from Ca2+ dysregulation and elevated protein phosphatase activity: a finding that has been subsequently demonstrated in numerous injury and disease models characterized by learning and memory deficits. His work as a postdoctoral fellow in Dr. Phil Landfield's laboratory at the University of Kentucky found that Ca2+-dysregulation and elevated phosphatase activity are not only intimately linked, but form a deleterious positive feedback cycle in aging brain. These investigations led to the unexpected discovery that astrocytes are a focal point of hyperactive Ca2+-dependent phosphatase (calcineurin) activity, highlighted by the intense upregulation of calcineurin in activated astrocytes of aging wild-type mice and transgenic APP/PS1 mice—especially in the immediate vicinity of amyloid deposits. After joining the faculty at the SBCoA in 2004, the Norris lab has investigated the impact of astrocyte activation, and hyperactive calcineurin signaling, on the progression of Alzheimer's pathophysiology using both human postmortem brain specimens and mouse models of amyloidosis. Experimental approaches commonly used in the Norris lab include: electrophysiology, multiphoton imaging, AAV-mediated gene delivery, protein biochemistry, gene expression analysis, and small rodent behavioral assessment. An ongoing R01 project, funded since 2006, has revealed key causative roles of astrocytic calcineurin/NFAT signaling on neuroinflammation, glutamate dysregulation, and synapse dysfunction associated with Alzheimer's pathology and small cerebrovessel disease.

Q134R: Novel Small Chemical Compound with NFAT Inhibitory Properties Ameliorates Synaptic Deficits in a Mouse Model of Alzheimer's Disease

Christopher Norris

University of Kentucky

Increased expression/activity of calcineurin (CN) and the CN-dependent transcription factor, NFAT, appears at early stages of cognitive loss and correlates to the progression of pathological and clinical features of Alzheimer's disease (AD). In AD mouse models, commercial CN inhibitors typically exhibit anti-inflammatory, anti-amyloid, neuroprotective, and/or nootropic properties. Genetic inhibition of NFATs in AD mouse models has similar beneficial effects, suggesting that the reduction of NFAT activity alone is sufficient for clinical efficacy. Here, we tested the NFAT-inhibiting properties and synapto-modulatory effects of the novel chemical compound, Q134R, developed by Avidin Biotechnology. Q134R is safe and well-tolerated in humans and provides neuroprotection in experimental models. In the present study, we found that Q134R inhibited NFAT activity in primary astrocytes and neurons but did not inhibit CN activity in vitro or in intact cells. Oral delivery (via gavage) of Q134R to mid aged APP/PS1 mice across a one-to-two-week period reduced GFAP volume, inhibited the nuclear localization of NFAT4 in hippocampal astrocytes, and improved performance on the Y maze. Long term (3 mos) oral administration of Q134R to APP/PS1 mice beginning at six-months-of-age improved basal synaptic strength and promoted the induction of long-term potentiation measured in ex vivo brain slices. In wild type mice, long-term oral administration of Q134R enhanced survival curves, but caused no obvious signs of systemic immunosuppression. The results demonstrate that Q134R inhibits hyperactive NFAT signaling en route to protecting synaptic function and cognition during the progression of AD-like pathology. The findings offer important proof-of-concept support for the use of small chemical NFAT inhibitors, like Q134R, in the treatment of AD and related neurodegenerative disorders.

Grace (Beth) Stutzmann, PhD—Rosalind Franklin University of Medicine and Science/NeuroLucent, Inc.

Grace Stutzmann, PhD, is an Associate Professor in the Department of Neuroscience at The Chicago Medical School/Rosalind Franklin University of Medicine and Science, where she studies early cellular mechanisms of Alzheimer's disease and is developing novel therapeutic approaches to treat neurodegenerative disorders.

Dr. Stutzmann received her PhD in Neuroscience from New York University/The Center for Neural Science in 1999. She then trained as a postdoctoral fellow in the Departments of Pharmacology and Psychiatry at Yale School of Medicine under George Aghajanian, MD, and then at UC Irvine in the Department of Neurobiology & Behavior, and The Institute for Brain Aging and Dementia with Frank LaFerla, PhD and Ian Parker, PhD, FRS.

In 2005, she moved to the Chicago Medical School as an Assistant Professor in the Department of Neuroscience, where she is currently. Dr. Stutzmann's research is and has been supported by the NIH, Alzheimer's Drug Discovery Foundation, the Alzheimer's Association, the American Federation for Aging Research, The Schweppe Foundation, and the VA.

Dr. Stutzmann has served on numerous NIH, foundation, and international review committees, as well as scientific advisory boards. She has presented over 60 lectures at international symposia and universities since 2006. Honors include fellowships from NIH, the Young Investigator Award from The Institute for Brain Aging and Dementia, The NeuroImaging Award from AFAR, and The Board of Trustees Award from RFUMS/CMS.

Inhibiting Ryanodine Receptors, an ER Calcium Channel, to Prevent Synaptic Pathology and Protein Mishandling

Grace (Beth) Stutzmann

Rosalind Franklin University of Medicine and Science/NeuroLucent, Inc.

In Alzheimer's disease, the primary outcome targeted in clinical trials is the preservation of memory functions. Loss of cognitive ability is the most feared aspect of AD, yet few if any clinical trials or therapeutic strategies are directly targeting the processes involved in memory encoding. Memory encoding initiates at synapses, the point of connection between neurons in which changes in synaptic strength serve as the earliest stages of memory formation and storage. One of the earliest features of AD pathology is synaptic loss within key memory regions of the brain, including the hippocampus and cortex. Not surprisingly, synaptic loss positively correlates with degree of cognitive impairment in AD, in contrast to highly targeted features such as beta amyloid.

Synaptic structure, function, and plasticity are strongly regulated by intracellular calcium signaling. In AD pathogenesis, increased calcium release through ER-localized ryanodine receptor channels are linked to all the major features of AD, including amyloid, tau, inflammation, and synaptic dysfunction and the associated memory impairments. Thus, this RyR channel is an ideal drug target to address a multitude of symptoms, not just a single phenotype. Previously, we and others have shown that normalizing RyR-Ca2+ signaling restores synaptic plasticity, reduces amyloid and tau histopathology, and improves memory performance in AD mouse models. Our current efforts are focused on developing novel CNS penetrant negative allosteric modulators of the brain isoforms of RyR to restore normal calcium levels and thus preserve synaptic function. Furthermore, we have expanded our model systems to include human neurons derived from AD patient fibroblasts to validate translational relevance and potential for clinical success. Our current library of novel compounds shows selective reduction in RyR-evoked calcium release in model cells with RyR2 defects, in mouse models of AD, and in human neurons from AD patients. Expanded studies in mouse models demonstrate the specific synaptic mechanisms restored by normalizing RyR-calcium signaling in neuronal compartments and reduces protein mishandling through intracellular organelles.

Shijun Zhang, PhD—Virginia Commonwealth University

Shijun Zhang, PhD, is currently a Professor of Medicinal Chemistry and the Graduate Program Director in the Department of Medicinal Chemistry, School of Pharmacy, Virginia Commonwealth University (VCU). Dr. Zhang also serves as the Board Member of Alzheimer's Association Greater Richmond Chapter.

Dr. Zhang received his BS in Pharmacy and MS in Medicinal Chemistry in 1993 and 1996 from Shandong Medical University, respectively. In 2000, he moved to the United States and received his PhD in Medicinal Chemistry and Pharmaceutical Sciences from Wayne State University in 2004. After his postdoctoral training at the University of Minnesota with Professor Portoghese, he joined the School of Pharmacy, VCU as a faculty where he was promoted to Associate Professor with tenure and to Professor.

The research in Dr. Zhang's group is focused on rational small molecule design for neurodegenerative diseases and inflammatory disease, particularly focusing on Alzheimer's disease, multiple sclerosis, and traumatic brain injury. Another area that his research group has actively engaged is the design of chemical probes into understanding the dysfunctions of inflammasomes and mitochondria in the pathogenesis of neurodegenerative disorders.

Design and Exploration of NLRP3 Inhibitors for Neurodegenerative Disorders

Shijun Zhang, PhD

Virginia Commonwealth University

Inflammasomes play a vital role in innate immunity via sensing both exogenous microbial products and endogenous host products that are associated with cellular stress and damage. The NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome is by far the most studied and characterized inflammasome. Activation of the NLRP3 inflammasome leads to maturation of the precursor forms of interleukin (IL)-1β and IL-18 into active proinflammatory cytokines and promotes inflammatory cell death. Notably, recent studies have indicated a critical role for the NLRP3 inflammasome and IL-1β in the pathogenesis of Alzheimer's disease (AD), where neuroinflammation has been recognized as an essential player. Thus, NLRP3 inflammasome represents an attractive target to develop small molecule inhibitors as chemical probes and potential disease modifying agents for AD. Our research laboratory has recently designed sulfonamide based small molecules as NLRP3 inhibitors. In the presentation, we will discuss the characterization of such small molecule inhibitors in AD models and mechanistic studies to shed light on their mode of action.

Thota Ganesh, PhD—Emory University

Thota Ganesh, PhD, obtained his MSc and PhD in chemistry from Osmania University, Hyderabad, India. Shortly after, he completed his postdoctoral studies at IIT-Bombay (India), University of Durham (UK) and Virginia Tech (USA).

Dr. Ganesh is now an Associate Professor in the Department of Pharmacology and Chemical Biology, at Emory University School of Medicine. Dr. Ganesh's current research interests are to develop chemical tools for biological targets. His current research focuses on developing small molecule agents to mitigate the inflammatory pathologies in neurodegenerative diseases, including epilepsy and Alzheimer's disease.

Dr. Ganesh is an author of more than 60 publications in peer-reviewed journals in the areas of medicinal chemistry, biochemistry and pharmacology.

Pharmacological Inhibition of EP2 Receptors Suppress Neuroinflammation in the Female 5xFAD Mice, but not in the Male 5xFAD Mice

Thota Ganesh

Emory University

The prostanoid receptor EP2 has emerged as an important target mediating pro-inflammatory function via induction of cAMP. Microglia lacking EP2 receptors show decreased phagocytosis of Aβ-load ex vivo, and conditional ablation of EP2 receptors in myeloid cells (Cd11b-Cre EP2fl/fl) showed enhanced clearance of Aβ and reduced functional and spatial memory deficits in APP-PS1 transgenic mice. Here, we asked whether pharmacological treatment of an EP2 antagonist would have any beneficial effects on neuroinflammation in the 5xFAD mouse model of Alzheimer's disease.

Male and female 5xFAD mice on C57BL/6 background along with the wild-type littermates were treated with a potent and selective EP2 antagonist, TG11-77HCl, (100 mg/kg/day, in drinking water) for 2 months starting at 3 months of age. These mice were also treated with a low-dose LPS (0.5 mg/kg, ip, once/week for 8 weeks) to induce a low-level inflammatory response in the brain. Chronic EP2 antagonist treatment reduced the mRNA level of inflammatory cytokines (IL-6, IL-1β, TNF-α), chemokines (CCL2, CXCL10) and glial markers (Iba1, GFAP, CD11b, S100B) in the cortex of female 5xFAD mice. The expression of Iba1 and GFAP were also reduced in other regions of the brain in the female 5xFAD mice. On the other hand, upregulation of the inflammatory mediators and glial markers in male 5xFAD was not significantly different from wild-type littermates. Therefore, chronic treatment with the EP2 antagonist did not show any additional effect on inflammatory gene expression in males. Complete blood count analysis indicated that LPS induced the peripheral inflammation in the blood and there was no effect of EP2 antagonist TG11-77.HCl on blood markers (RBC, lymphocytes, monocytes, neutrophils, and platelets and other blood markers) suggesting its effects measured in the brain likely reflect a central nervous system action.

SESSION II: NOVEL APPROACHES FOR FRONTOTEMPORAL DEMENTIA
Chair: Meriel Owen, PhD—Alzheimer's Drug Discovery Foundation

Meriel Owen, PhD, is a member of the ADDF's Scientific Affairs team. She supports the scientific portfolio through strategic review and program management.

Dr. Owen earned her doctorate in neuroscience from Northwestern University, where she used neuroimaging and robotic techniques to better understand the neural mechanisms underlying motor impairment after stroke. She received a MSc from University College London in clinical neuroscience and a bachelor's degree in cognitive science from the University of California, Berkeley. Dr. Owen is also interested in the intersection between neuroscience and entrepreneurship.

During her graduate studies, she completed the Kellogg Management Program for scientists and engineers, was selected as a Northwestern Leadership Fellow, and co-founded a startup company that won the Neuro Startup Challenge.

TDP-43 Proteinopathies: Challenges and Opportunities for a Pathology-specific Biofluid Test
Mari DeMarco, PhD—University of British Columbia

Novel Human FTLD Neuron and Microglia Cell Models for Drug Discovery
Steven Finkbeiner, MD, PhD—Gladstone Institutes/University of California, San Francisco

Blood Biomarker Monitoring in Frontotemporal Lobar Degeneration
Rodney Pearlman, PhD—The Bluefield Project to Cure FTD

Non-Invasive Brain Stimulation to Restore Cortical Plasticity in FTD
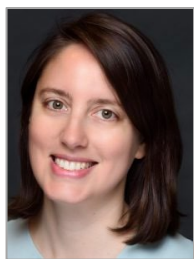Alberto Benussi, MD—University of Brescia

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EMERGING CONCEPTS: DATA BLITZ

Young Investigator #1: Shanshan Wang, MD, PhD, University of CA, San Diego

Young Investigator #2: Christina Tognoni, PhD, Boston University/VA Boston Healthcare System

Young Investigator #3: Nicole Kasica, PhD (cand.), Wake Forest University

Mari DeMarco, PhD—University of British Columbia

Dr. DeMarco, is a clinical chemist at St Paul's Hospital, and a clinical associate professor in the Department of Pathology and Laboratory Medicine at the University of British Columbia in Vancouver, Canada. Dr. DeMarco earned a PhD in Medicinal Chemistry from the University of Washington, as part of the Biomolecular Structure and Design Program. She subsequently completed a Clinical Chemistry fellowship at Washington University School of Medicine.

With a strong interest in bridging basic biomedical science, analytical chemistry and laboratory medicine, Dr. DeMarco's research group focuses on building new biofluid tests for direct translation into patient care. A particular area of interest is advancing protein-based clinical diagnostics for neurodegenerative disorders, such as Alzheimer's disease and frontotemporal dementia. Critically, the goal of this program of research is to ensure that these new tools make the challenging jump from the research setting to the health care system.

TDP-43 Proteinopathies: Challenges and Opportunities for a Pathology-Specific Biofluid Test

Mari DeMarco

University of British Columbia

TDP-43 is a 414-residue nuclear protein that is ubiquitously expressed in almost all tissues. Its functions include producing transcription variants, and regulation of RNA stability, transport, splicing, translation, and processing. While the exact role of TDP-43 in the pathobiology of neurodegenerative disorders, including FTD and ALS, remains elusive, post-translational modifications of TDP-43 have been identified in higher abundance in affected versus unaffected human tissues. The existence of a range of phosphorylated, ubiquitinated, and truncated forms of TDP-43 in the pathological protein deposits are encouraging from a biomarker development standpoint, as they suggest a disease-specific TDP-43 signature in TDP-43 proteinopathies. The challenges and opportunities for such a TDP-43-specific biofluid marker will be discussed, as will our efforts to develop analytical approaches – beyond ligand binding methods – that can monitor and quantify changes in TDP-43 sequence and structure in human tissues and fluids.

Steven Finkbeiner, MD, PhD—Gladstone Institutes/University of California, San Francisco

Steve Finkbeiner, MD, PhD, is Director of the Center for Systems and Therapeutics and Taube/Koret Center for Neurodegenerative Disease Research at Gladstone Institutes, and is a Professor of Neurology and Physiology at the University of California, San Francisco. Dr. Finkbeiner earned a bachelor's degree from Wheaton College, and concurrently earned an MD and a PhD in neuroscience from Yale University. He completed an internship in internal medicine and chief residency in neurology at the University of California, San Francisco, followed by a research fellowship at Harvard Medical School.

Dr. Finkbeiner's academic research laboratory has focused on understanding the causes and finding treatments for ALS, AD, HD, PD and other neurological and psychiatric disorders. The laboratory pursues these goals through the use of genomics, induced pluripotent stem cells, artificial intelligence and robotic microscopy, which they invented, and is engaged in myriad collaborations with others in academia and pharma/biotech.

Human Microglial and Neuronal Models of Frontotemporal Dementia and Strategies to Rescue Progranulin Haploinsufficiency

Steven Finkbeiner

Gladstone Institutes/University of California, San Francisco

Progranulin-haploinsufficiency causes frontotemporal dementia (FTD) and variants at the progranulin locus may increase the risk of Alzheimer's disease (AD). Abnormal microglial activation is neuropathological hallmark of both disorders, and genome-wide association studies of AD patients suggest that a number of genetic variants that confer risk of AD occur in genes expressed in microglia. Here we describe the establishment of human cell models of FTD including microglia and neurons developed from patient derived induced pluripotent stem cells, which display progranulin deficiency and disease-associated phenotypes. These models form part of our preclinical platform, which includes in vivo mouse models, that we are using to develop therapeutic targets and small molecules for frontotemporal dementia.

Rodney Pearlman, PhD—The Bluefield Project to Cure FTD

Rodney Pearlman, PhD, is President of The Bluefield Project to Cure Frontotemporal Dementia. Bluefield is a non-profit medical research foundation based in San Francisco that manages a consortium of 20 researchers focused on developing treatments for FTD.

Previously, Dr. Pearlman was President and CEO of Nuon Therapeutics, a company developing drugs for treating diseases of the immune system and inflammation. Prior to joining Nuon, he was a co-founder, President and CEO of Saegis Pharmaceuticals, developing treatments for Alzheimer's disease mild cognitive impairment and schizophrenia until its acquisition by H. Lundbeck A/S. Dr. Pearlman held previous positions at the gene therapy company Valentis and was Director of Pharmaceutical Research and Development at Genentech, where he and his group developed novel formulations, processes and delivery systems for recombinant human proteins. He also was the Project team Leader for Nutropin® human growth hormone through its NDA approval.

Prior to that, Dr. Pearlman taught at the University of Texas in Austin and was previously a Senior Scientist with Eli Lilly and Company. Dr. Pearlman received his PhD in pharmaceutical chemistry from the University of Kansas with Prof. Takeru Higuchi on the delivery of drugs to the brain. He received his BPharm from the Victorian College of Pharmacy, Monash University, Melbourne, Australia.

Blood Biomarker Monitoring in Frontotemporal Lobar Degeneration: the Neurofilament Light Surveillance Project (NSP)

Rodney Pearlman

The Bluefield Project to Cure FTD

Frontotemporal Lobar Degeneration (FTLD) is a currently untreatable neurodegenerative disease with both sporadic and familial origins. Familial FTLD (f-FTLD) is caused primarily by inherited mutations in three genes (C9ORF72, GRN and MAPT) and has generated significant interest in development of therapeutic strategies. Indeed, several clinical trials are ongoing in f-FTLD and a number of new trials are imminent. Consequently, there is a pressing need for validated peripheral biomarkers for trial enrichment and quantification of patient response to intervention.

ALLFTD, an NIH-funded clinical research consortium, is collecting natural history data on both asymptomatic and symptomatic FTLD mutation carriers and family members via participants' annual visits to one of 19 participating North American clinical sites. Recent studies indicate that the axonal protein neurofilament light (NfL) may be a promising marker of FTLD disease onset, severity and future decline. Longitudinal ALLFTD data indicate plasma NfL levels may reliably predict conversion from asymptomatic to symptomatic disease in f-FTLD.

To better understand how peripheral NfL levels change in f-FTLD, we assembled a pre-competitive, public-private partnership called the Neurofilament light Surveillance Project (NSP), involving patient advocacy groups, NIH-funded academic FTLD researchers and pharmaceutical and biotech companies. The NSP is a sub-study of ALLFTD. Participants enrolled in the NSP will donate blood at home via visits from traveling research nurses four times a year for three years, thus enabling us to observe peripheral NfL levels longitudinally during disease onset and progression. This higher resolution readout will enhance our understanding of NfL's utility as a prognostic biomarker and enable its potential use as a response biomarker in clinical trials.

Alberto Benussi, MD—University of Brescia

Alberto Benussi, MD, is a researcher in the Department of Clinical and Experimental Sciences at the University of Brescia, Italy. He has focused his scientific interest in the application of non-invasive brain stimulation techniques in patients with neurodegenerative diseases, particularly in Alzheimer's disease, sporadic and genetic forms of frontotemporal dementia, atypical parkinsonisms and rare diseases, such as Niemann-Pick type C disease and several forms of hereditary and sporadic ataxias. In this context, Dr. Benussi has implemented and developed several neurophysiological protocols of transcranial magnetic stimulation, identifying several biomarkers of cortical connectivity both for the differential diagnosis of various neurodegenerative disorders, and as preclinical biomarkers of disease. Moreover, he has conducted several clinical trials using non-invasive brain stimulation techniques applied to different neurodegenerative disorders. The applications of these methods have been acquired in Italian and foreign centers of excellence.

Non-Invasive Brain Stimulation to Restore Cortical Connectivity in FTD

Alberto Benussi

University of Brescia

Clinical trials in FTD currently lack reliable biomarkers to identify disease progression, particularly in the presymptomatic phases of disease. Recently, biomarkers of cortical connectivity, assessed by transcranial magnetic stimulation (TMS), have shown to be impaired nearly 18 years before expected symptom onset in presymptomatic patients bearing a pathogenic mutation for FTD. Furthermore, these biomarkers reflect disease progression not only in the presymptomatic phases of disease but also in the symptomatic phases.

The goal of this study is to evaluate the effects of transcranial direct current stimulation (tDCS) on the frontal and prefrontal cortex in presymptomatic and symptomatic monogenic FTD, as well as in sporadic FTD patients, including behavioral variant FTD and the primary progressive aphasias (PPA).

Twenty presymptomatic at risk subjects bearing a pathogenic GRN mutation, twenty symptomatic FTD bearing a pathogenic GRN mutation, and thirty symptomatic sporadic FTD patients with a bvFTD or avPPA phenotype were recruited and underwent left-frontal tDCS in a randomized double-blind, sham-controlled study. Patients were evaluated with a complete neuropsychological and neurophysiological evaluation at T0, at 2-weeks post stimulation (T1), three-months post-stimulation, (T2) and at six-months follow-up (T3).

We observed a significant interaction between TIME and TREATMENT on cognitive performances and caregiver burden scores ($p<0.05$) with a significant improvement in both scores after real stimulation. Moreover, we observed restoration of intracortical inhibition and facilitation mechanisms in the frontal cortex (SICI and ICF respectively, $p<0.001$), outlasting the intervention phase for over 3 months, while sham tDCS did not significantly modify any neurophysiological measures.

These results suggest a long-term modulation of the frontal cortex by means of tDCS, which could restore physiological parameters of intracortical inhibition and facilitation, thus improving cognitive functions and caregiver burden in patients with both genetic and sporadic FTD.

EMERGING CONCEPTS: DATA BLITZ

Shanshan Wang, MD, PhD—University of CA, San Diego

Shanshan Wang, MD, PhD, is a postdoctoral Researcher at the VA San Diego Healthcare System. Her main interest is to use genetic interventions (via viral vector gene therapy) to regenerate neuronal growth after traumatic brain injury (TBI), in the aging brain and neurodegenerative disease (e.g. ALS and Alzheimer's Disease). Her research focuses on how caveolin, a scaffolding protein in membrane/lipid rafts (MLRs), regulates synaptic signaling and neuroplasticity in vitro and in vivo. Her group utilizes a viral vector (AAV) that contains a neuron-targeted promoter (synapsin) to drive the expression of caveolin-1 (Cav-1) specifically in neurons after injury or during neurodegenerative conditions. They are currently testing the therapeutic efficacy in rodent models of AD. In addition, she also did research on the underlying mechanisms of neuroplasticity in the human AD neurons that derived from IPSCs.

Neuron-targeted Caveolin-1 Preserves Hippocampal Neuroplasticity and Memory in AD Mice

Alzheimer's disease (AD) is a neurodegenerative condition with severe cognitive deficits and is closely associated with loss of synapses and decreased plasticity. Targeting neuroprotective mechanisms specifically to neuronal cells may restore functional neuronal and synaptic plasticity independent of removing toxic amyloid species. Here we show that a one-time hippocampal administration of adeno-associated virus that encodes neuron-targeted Cav-1 using a synapsin promoter (AAV-SynCav1) at 3 months (m) preserves learning and memory in 9 and 11 m old amyloid-positive APPSwePS1d9 mice (i.e., AD). Microscopy showed preserved hippocampal dendritic arbor and preserved ultrastructural indicators of synaptic plasticity (total synapses, presynaptic vesicles per axonal bouton, dendritic spine morphology) on CA1 apical dendrites, and preserved myelination of CA3 Schaffer collaterals in 9 and 11 m AD-SynCav1 mice. Proteomic analysis of membrane/lipid raft fractions (MLRs) revealed decreased Shisa9 (an AMPAR regulatory protein critical for memory) in AD-SynRFP, which was restored in AD-SynCav1. Cav-1 immunoprecipitation (IP) of MLRs from AD-SynCav1 mice revealed strong Shisa9 expression compared to AD-SynRFP, thus confirming the proteomic results. This study shows the potential of neuron-targeted Cav-1 (i.e., SynCav1) gene delivery to restore plasticity and higher brain function in amyloid-positive AD mice, through restoration of MLR-associated Shisa9.

Christina Tognoni, PhD—Boston University / VA Boston Healthcare System

Christina Tognoni, PhD is a postdoctoral researcher at the VA Boston Healthcare System in Jamaica Plain, MA and affiliated instructor at the Boston University School of Medicine in the department of Neurology. Dr. Tognoni graduated with a Bachelor of Arts degree in Neuroscience and Spanish from Wellesley College in the town of Wellesley, MA and, as an NSF Graduate Research Fellowships Program (GRFP) fellow, earned her doctorate in Systems & Integrative Neuroscience at Duke University in Durham, NC. She began her postdoctoral work as a fellow under the Boston University Alzheimer's Disease Center's NIH T32 postdoctoral training grant and has continued her research in the Translational Neurotherapeutics Laboratory at the VA Boston Healthcare System and Boston University Neurology Department under mentorship of Dr. Alpaslan Dedeoglu. Her approach to studying Alzheimer's disease encompasses brain to behavioral measures using mouse models to examine the extent to which treatments or risk factors alter outcomes, considering the interactions of neural, vascular, cholinergic, endocrine, and immune systems. Dr. Tognoni's recent research focuses on sphingosine-1-phosphate receptor modulators as a therapy in Alzheimer's disease model mice at early and late stage disease.

Treatment with AUY954, a Selective Sphingosine-1-Phosphate Receptor 1 Agonist, Reduces Early Development of Aβ Pathology and Neuroinflammation in a Mouse Model of Alzheimer's Disease

The brains of Alzheimer's disease (AD) patients have abnormal lipid metabolism that includes increased accumulation of sphingosine and reduced levels of sphingosine-1-phosphate (S1P) that correlates with the accumulation of amyloid

beta (Aβ). S1P acts through a family of G protein-coupled receptors (S1PR1-5) that are expressed by cells in tissues including the brain and are involved in a variety of cellular functions, including cell proliferation, cell survival, angiogenesis, immune cell trafficking, and anti-inflammatory responses. Fingolimod is a structural analog of sphingosine that, when phosphorylated, can activate all S1PRs except S1PR2 and is an effective FDA-approved treatment for relapsing-remitting multiple sclerosis, although the mechanism is thought to be due to its effects on S1PR1 that prevent lymphocyte egress from the lymph nodes. We recently have demonstrated that fingolimod treatment in the 5xFAD transgenic mouse model of AD provides neuroprotection and reduces neuroinflammation, optimally at low doses that do not diminish peripheral lymphocyte counts. Here we investigated if targeting only S1PR1 with the novel selective receptor agonist AUY954 could effectively ameliorate AD-associated pathology and neuroinflammation. We conducted a dose-response study using AUY954 administered orally through drinking water at doses 0.01-0.3 mg/kg/day in 5xFAD mice from 1-3 months of age. Even at the highest dose used, peripheral blood lymphocytes were not significantly decreased. in a dose-dependent manner, AUY954 treatment was able to reduce Aβ40 and Aβ42 levels (as measured by ELISA), plaque burden (Aβ42 immunostaining), microglia densitometry (Iba1 immunostaining), reactive astrocytes (GFAP immunostaining), and pro-inflammatory chemokines and cytokines (multiplex immunoassay) compared to untreated 5xFAD mice. Together these findings show that AUY954 is capable of ameliorating both neuroinflammation and Aβ accumulation at low doses and suggest that S1PR1 may be a potent therapeutic target in AD.

Nicole Kasica, PhD (cand.)—Wake Forest University

Nicole Kasics, PhD, is a 4th year Neuroscience PhD candidate in the lab of Tao Ma, MD, PhD at Wake Forest University. Her research focuses on the role of protein synthesis in Alzheimer's Disease, with her thesis focusing on the therapeutic potential of eEF2K inhibitors in a mouse model of AD.

Memory Impairments and Synaptic Failure in Tg19959 AD Model Mice are Alleviated by Eef2k Inhibitor A-484954

Mounting evidence indicates synaptic failure as an early and key event in Alzheimer's Disease (AD) pathophysiology. Maintenance of long-term memory and synaptic plasticity requires de novo protein synthesis. Phosphorylation of mRNA translation factor eukaryotic elongation factor 2 (eEF2) by its kinase eEF2K results in inhibition of general protein synthesis. Previous studies have shown elevated levels of eEF2 phosphorylation in post mortem AD human brain tissue and in AD mouse models. Here we investigated whether suppression of eEF2 phosphorylation via eEF2K inhibitor A-484954 can alleviate AD-associated synaptic failure and memory impairments. Aged Tg19959 mice (6-9 months) and age-matched controls were treated with a subcutaneous pellet containing A-484954 or vehicle. the pellet continuously releases treatment over 30 days. Starting two weeks after pellet placement, the mice underwent cognitive assessment via the Novel Object Recognition (NOR) and Morris Water Maze (MWM). We found that cognitive impairments displayed in aged Tg19959 mice were alleviated with treatment of A-484954. Furthermore, de novo protein synthesis was assessed via the surface sensing of translation (SUnSET) assay, and it was found that levels of de novo protein synthesis were rescued in Tg19959 mice treated with A-484954. Spine morphology and post-synaptic density (PSD) formation were analyzed using Golgi staining and electron microscopy, respectively. Tissue and blood samples from these mice also underwent high performance liquid chromatography (HPLC) to assess drug concentrations in various locations of the body. Taken together, our results suggest that treatment with a eEF2K inhibitor, NH125, alleviates cognitive impairments and restores translational capacity in a mouse model of AD.

SPECIAL SESSION SPEAKER
Zane Martin, PhD—NIA

Zane Martin, PhD, is Program Director for Alzheimer's Disease and Related Dementias Translational Research in the Division of Neuroscience at the National Institute on Aging (NIA). She oversees SBIR and STTR grants focused on drug discovery, drug development, and clinical trials aimed to ameliorate various dementias of aging.

Before being hired as Program Director, Dr. Martin was a AAAS Science & Technology Policy Fellow at NIA. During that time, she was awarded the National Institutes of Health Award of Merit for helping with the development and implementation of the Alzheimer's Disease Preclinical Efficacy Database (AlzPED). AlzPED is a publicly available data resource that aims to increase reproducibility, transparency, and translatability of preclinical Alzheimer's drug discovery studies with the goal of improving the drug pipeline to human clinical trials. Dr. Martin has a PhD in Neuroscience and MS in Pharmacology from the University of Texas Medical Branch. She received postdoctoral training in the Department of Neurochemistry at the New York State Institute for Basic Research in Developmental Disabilities.

Her research career has primarily focused on drug discovery strategies to combat Alzheimer's disease and related dementias. She has investigated a wide range of therapeutic targets, including tau hyperphosphorylation, synaptic dysfunction, and amyloid aggregation.

National Institute on Aging's Alzheimer's and Related Dementias Translational Research Funding Opportunities

Zane Martin

NIA

This talk will provide an overview of the NIA Alzheimer's and Related Dementias (AD/ADRD) Translational Research Program including current funding opportunities and initiatives available to investigators. A particular focus will be on NIA AD/ADRD translational small business SBIR/STTR programs, with details on eligibility requirements, budget specifics, and technical and entrepreneurial assistance opportunities. The final part of the talk will outline tips on applying for a NIH grant.

KEYNOTE SPEAKER

Sabrina Paganoni, MD, PhD—Massachusetts General Hospital/Harvard University

Sabrina Paganoni, MD, PhD, is an Assistant Professor at Harvard Medical School and works as a physician scientist at the Healey Center for ALS at Massachusetts General Hospital. Dr. Paganoni's research focuses on therapy development for ALS. She designed and is currently leading several ALS clinical trials that include novel endpoints and biomarkers and innovative trial designs. She is currently working on the first Platform Trial for ALS.

Dr. Paganoni received her medical degree from the University of Milan, Italy, and her PhD in Neuroscience from Northwestern University. She completed her residency and fellowship training in Boston in the Harvard Medical School hospital system. Dr. Paganoni published >70 peer-reviewed papers. Her research has been funded by the NIH, foundations, and industry. She received several awards for her work including the NIH Rehabilitation Medicine Scientist Training Program Award (2012), the American Academy of Neurology/ALS Association Three-Year Career Development Award in ALS (2017), and the American Association of Neuromuscular & Electrodiagnostic Medicine Scientific Impact Award (2019).

The Use of Platform Trials in CNS Disorders

Sabrina Paganoni

Massachusetts General Hospital/Harvard University

Exponential progress in our understanding of the pathophysiology of several CNS disorders has led to the development of a large pipeline of investigational products. This context creates the urgent need to innovate our clinical trial strategies to test several agents in a time- and cost-effective manner. Platform trials are a transformative approach with operational and scientific advantages and are viewed favorably by regulators and sponsors. Platform trials can also create opportunities to study novel biomarkers and outcome measures in a clinical trial setting thus driving science and accelerating the path to effective treatments. This talk will present the development and launch of the first platform trial for amyotrophic lateral sclerosis (ALS). The HEALEY ALS Platform Trial is the result of an active collaboration among international ALS clinical trial experts, scientists and statisticians, with input from patients and caregivers. The initial call for therapeutic ideas was issued in March 2019. The first three investigational products were selected in June 2019 from a large number of nominations. Several other promising agents have been identified and could enter the platform soon after the first set of three. Given the broad interest from industry, investigators and the ALS patient community, therapy nominations will continue to be accepted on a rolling basis. Up to 60 NEALS consortium sites were selected and, at present, the trial is in the start-up phase. The trial will leverage a shared infrastructure with central governance, central Institutional Review Board (IRB), and uniform data and sample collection processes and will be conducted under a Master Protocol. In addition to traditional clinical measures of function, the trial has been designed as an Endpoint Development Engine to better understand the performance of novel ALS biomarkers and outcome measures such as analyses of speech and neurofilament levels. Furthermore, systematic collection of bio-samples will facilitate drug-specific target engagement assays as applicable and additional biomarker discovery efforts. Whole genome sequencing will be obtained for all study participants. The adaptive, perpetual nature of the trial will make it possible to continue to refine the trial design and to adapt to more efficient measures of disease progression as they become available. The Platform Trial will energize the ALS community, drive development of novel outcome measures and biomarkers, provide data and samples for future discovery, and expand options for ALS treatment.

SESSION III: CLINICAL TRIALS IN ALZHEIMER'S DISEASE

Chair: Alessio Travaglia, PhD—Alzheimer's Drug Discovery Foundation

Alessio Travaglia, PhD, is a member of the ADDF's Scientific Affairs team. He supports the scientific portfolio through strategic review of proposals and program management.

Dr. Travaglia completed his postdoctoral training at New York University, where he studied mechanisms underlying memory formation during infancy. He earned a doctorate in nano science at the University of Catania (Italy), where he worked on synthesis and characterization of new potential drugs for Alzheimer's disease. Dr. Travaglia has authored numerous peer-reviewed publications, including articles in Nature Neuroscience and Journal of Neuroscience.

Rasagiline Rescue (R2): A Double-Blind Placebo Controlled Trial for Mild to Moderate Alzheimer's Disease
Jeffrey Cummings, MD, ScD—Cleveland Clinic

Clinical Biomarker Evidence for Target Engagement, Reduction of Synaptic Damage and Disease Modification in Alzheimer's Patients Treated with CT1812 (Elayta™)
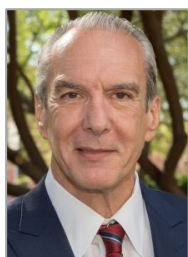Susan Catalano, PhD—Cognition Therapeutics

Vafidemstat: The First Epigenetic Approach in Alzheimer's Disease
Roger Bullock, MBBS—Oryzon

Vascular Approaches for Alzheimer's Treatment
Ihab Hajjar, MD—Emory Health Care

Jeffrey Cummings, MD, ScD—Cleveland Clinic

Jeffrey Cummings, MD, ScD, is Vice Chair of Research, UNLV Department of Brain Health. He is Founding Director of the Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Nevada, and Professor of Medicine (Neurology), Cleveland Clinic Lerner College of Medicine of Case Western Reserve University. Dr. Cummings is Principal Investigator/Director of the NIH/NIGMS-funded Center for Neurodegeneration and Translational Neuroscience.

Dr. Cummings is a world-renowned Alzheimer's researcher and leader of clinical trials. He has been recognized for his research and leadership contributions in the field of Alzheimer's disease through the Henderson Award of the American Geriatrics Society (2006), the Ronald and Nancy Reagan Research Award of the national Alzheimer's Association (2008), and the Lifetime Achievement Award of the Society for Behavioral and Cognitive Neurology (2017). In 2010, he was honored by the American Association of Geriatric Psychiatry with their Distinguished Scientist Award. In 2018, he was honored with the Leadership and Achievement Award by the International Society of CNS Drug Development, and he received the Bengt Winblad Lifetime Achievement Award from the national Alzheimer's Association. In 2019, he received the Alzheimer's Drug Discovery Foundation's Melvin R. Goodes Prize that honors an innovative researcher who has made a significant and lasting impact in the field.

Dr. Cummings completed Neurology residency and a Fellowship in Behavioral Neurology at Boston University, Boston, Massachusetts. US training was followed by a Research Fellowship in Neuropathology and Neuropsychiatry at the National Hospital for Nervous Diseases, Queen Square, London, England. Dr. Cummings was formerly Augustas Rose Professor of Neurology and Professor of Psychiatry at UCLA, Director of the Mary S. Easton Center for Alzheimer's Disease Research at UCLA, and Director of the Deane F. Johnson Center for Neurotherapeutics at UCLA. He is past president of the Behavioral Neurology Society and of the American Neuropsychiatric Association.

Dr. Cummings has authored or edited 43 books and published over 750 peer-reviewed papers.

Rasagiline Rescue (R2): A Double-Blind Placebo Controlled Trial for Mild to Moderate Alzheimer's Disease

Jeffrey Cummings

Cleveland Clinic

An exploratory Phase II clinical trial was conducted to evaluate the potential benefit of rasagiline, a selective monoamine oxidase B (MAO-B) inhibitor used in treatment of Parkinson's disease (PD), in patients with mild to moderate Alzheimer's disease (AD).

The primary objective was to determine if exposure to 1 mg of rasagiline once daily is associated with improved regional brain metabolism compared to placebo after a 24-week double blind study treatment in patients with mild to moderate AD. Secondary objectives were to evaluate: efficacy of rasagiline compared to placebo on cognition (ADAS-Cog 11), activities of daily living (ADCS-ADL), global function (CGIC), and neuropsychiatric symptoms (NPI); efficacy of rasagiline compared to placebo on measures of executive function (Digit Span test and COWAT for verbal fluency); safety and tolerability; correlation of FDG-PET results to flortaucipir PET findings; and the relationship of flortaucipir imaging to clinical measures.

The study design was a 24-week, double blind, parallel group, placebo controlled, randomized Phase II trial of 50 participants randomized in a 1:1 ratio at baseline to receive rasagiline or placebo for 24 weeks followed by a 4 week follow up. Subject inclusion was based on a clinical diagnosis of probable AD, age 50 to 90, MMSE 11 to 26, and likelihood of AD based upon evidence of an AD-like FDG PET pattern at screening.

The primary outcome of the study was positive: rasagiline treated subjects showed less decrease (less worsening) than placebo treated subjects in prespecified cortical regions including middle frontal cortex (left $p<0.012$, bilateral $p<0.04$), anterior cingulate ($p<0.04$), superior frontal cortex ($p<0.053$), and striatum, with slightly but not significantly less worsening in posterior cingulate-precuneus, inferior parietal, medial temporal, and lateral temporal regions. All mean clinical endpoint changes suggested a favorable outcome for rasagiline compared to placebo except ADL, in which trajectories were comparable between drug and placebo. Differences between rasagiline and placebo reached significance in QoL-AD ($p<0.04$) and trend for COWAT ($p<0.08$). Results indicated that modest subject numbers (48 and 112 per arm) would be required to demonstrate significance in ADAS-Cog and ADL at $p<0.05$, 80% power. Change in QOL-AD was positively correlated with change in anterior cingulate FDG SUVR ($R = 0.47$, $p < 0.002$). Longitudinal flortaucipir values exhibited measurement stability and showed increase in cortical regions in some subjects in both study arms, while uniform decreases were observed in striatum in the rasagiline arm. Rasagiline was well tolerated.

Study outcomes illustrated the potential for rasagiline to provide clinical benefit in AD patients and suggested that benefit is related to effects upon frontostriatal neuronal function as demonstrated by FDG PET. If benefit is confirmed in a larger population, the ability to add an existing medication to the limited armamentarium available to treat later stage patients could provide societal value at minimal cost. Results demonstrated the utility of a proof-of-concept design using imaging biomarkers for patient inclusion and as an outcome as a path to increase the probability of success of later stage AD trials.

Susan Catalano, PhD—Cognition Therapeutics

Susan Catalano, PhD, is the founder of Cognition Therapeutics and architect of its proprietary and unique biological discovery platform that is based on unbiased phenotypic screens in the target cell population of mature primary neurons. Using her 15 years of industry experience, Dr. Catalano and her team discovered and developed the company's drug candidate Elayta (CT1812), currently in clinical testing for the treatment of patients with mild-to-moderate Alzheimer's disease.

Prior to founding Cognition Therapeutics, Dr. Catalano was director of discovery biology for Acumen Pharmaceuticals, leading the team that discovered Acumen's lead candidates targeting Aβ oligomers. Earlier at Rigel, she led the team that pioneered the use of high content phenotypic screening to discover the Aurora kinase inhibitor R763. In scientific leadership roles within the neurophysiology and neuroimaging groups at Roche Palo Alto she led exploratory programs against targets involved in anxiety, depression and schizophrenia.

Dr. Catalano received her PhD from University of California, Irvine and postdoctoral training at University of California, Berkeley with Dr. Carla Shatz and at Caltech with Drs. Mary Kennedy and Scott Fraser studying the neurobiology of synaptic plasticity.

Clinical Biomarker Evidence for Target Engagement, Reduction of Synaptic Damage and Disease Modification in Alzheimer's Patients Treated with CT1812 (Elayta™)

Nicholas J Izzo (1), Kelsie Mozzoni (1), Anthony O. Caggiano (1), Lon S Schneider (3), Michael Grundman (1,2), Steven T. DeKosky (4), Ian Pike (5), Susan M. Catalano (1)

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CT1812 (Elayta™) is a novel, clinical stage, experimental Alzheimer's therapeutic that displaces synaptotoxic Aβ oligomers from their receptors. The Aβ oligomer hypothesis of Alzheimer's disease states that AD pathogenesis is initiated when Aβ oligomers bind specifically to a receptor site at synapses on neurons, initiating a series of downstream changes including activation of multiple kinases leading to abnormal localization and phosphorylation of tau at several amino acid sites, eventually resulting in synapse loss and damage. Cognition Therapeutics discovered that the sigma-2 receptor complex regulates the Aβ oligomer receptor site. CT1812 binds to and allosterically modulates the sigma-2 complex, which in turn destabilizes the Aβ oligomer binding site within the oligomer receptor complex, resulting in an increased off-rate of oligomers. CT1812 treatment results in increased Aβ oligomer concentration within the interstitial brain fluid, as well as in the cerebrospinal fluid (CSF) of huAPPSwe/Ldn Alzheimer's mice, consistent with clearance from the brain. CT1812's displacement of oligomers from their receptor returns oligomer-induced toxic changes to normal. CT1812 restores membrane and protein trafficking deficits, stops spine and synapse loss in vitro, and improves cognitive deficits in transgenic mouse AD models. CT1812 demonstrated a favorable clinical safety profile in healthy volunteers. A 28 day, multicenter, double-blind, placebo-controlled trial was performed with once daily CT1812 (90, 280 or 560 mg) or placebo (N = 4 or 5 group) administered p.o. to AD patients (MMSE 18-26). Plasma and CSF protein, lipid and metabolite values were measured at baseline and 28 days via ELISA or tandem mass spectroscopy. CSF Aβ oligomer concentrations were increased at day 28 relative to baseline in CT1812-treated compared with placebo-treated patients. Concentrations of CSF proteins and plasma proteins and lipids known to be dysregulated in AD changed in a therapeutic direction in CT1812-treated vs. placebo-treated patients. Synaptic protein fragments neurogranin and synaptotagmin were decreased in CSF at day 28 relative to baseline in the CT1812-treated compared to the placebo group. Detailed mass spectrometry analysis of soluble tau in CSF measured both unphosphorylated and phosphorylated protein and can reliably quantify ~35 of the 39 reported phosphosites on soluble tau in AD patient CSF (Russell et al 2017). Based on noise distribution we selected a minimum (up or down-regulation) of 30% difference in concentration between treated and placebo groups at each phosphosite for subsequent analysis. A prior study using this method (Russell et al 2017) concluded that 11 out of 35

phosphorylation sites increased by at least 30% in concentration in AD patients compared to age-match cognitively normal individuals. In the present study, the concentration of unphosphorylated tau did not change with CT1812 treatment, however 6 out of 33 quantified phosphorylation sites decreased by at least 30% in concentration in CT1812-treated compared to placebo-treated AD patients. These results suggest that CT1812 reduces tau kinase activity but has no impact on tau expression and is consistent with the observed reduction of synaptic damage. This is the first clinical evidence of a broad reduction in tau phosphorylation at a number of amino acid sites, supporting the Aβ oligomer hypothesis of AD. These clinical data support CT1812's mechanism of action of displacing Aβ oligomers, and provide evidence of target engagement, reduction of synaptic damage, and disease-modification. Ongoing trials include PET assessment of synaptic density, measures of synapse damage markers, and cognitive assessments.

Roger Bullock, MBBS—Oryzon

Roger Bullock, MBBS, is a licensed psychiatrist with more than 30 years of clinical experience. Dr. Bullock is widely published in the areas of Alzheimer's disease, dementia, and memory loss, and serves as a scientific consultant for Bioclinica's Alzheimer's research studies.

Dr. Bullock completed his pre-clinical medical training at Keble College, Oxford University, gaining a BA (Hons) Physiological Sciences in 1978 (converted to MA in 1985). This was followed by clinical medical training at St Bartholomew's Hospital in London where he gained the MB.BS in 1981.

In 1990, Dr. Bullock specialized in psychiatry, gained membership of The Royal College of Psychiatry and undertook postgraduate psychiatric training including higher specialist training in geriatric psychiatry which concluded in 1993.

Dr. Bullock is committed to research, particularly in psychopharmacology, neuropsychology, and the use of both in all areas of care. He believes that clinical trials not only benefit his current patients but will be of benefit to further patients in the future. He also feels that trials improve the service, introducing additional rigor to clinical practice.

Vafidemstat: The First Epigenetic Approach in Alzheimer's Disease

Roger Bullock

Oryzon

This presentation will focus on the close collaboration between Oryzon Genomics SA and the ADDF, highlighting the major steps taken with each grant and demonstrating how the scientific findings have been used to move vafidemstat into the clinical stage. After a brief recap of relevant preclinical and phase I data, the main focus will be on the current phase IIa programs, ETHERAL and REIMAGINE. Encouraging data will be presented and discussed to demonstrate how our clinical development plan is evolving and there will be an update on the progress of these studies. ETHERAL will be ready to present results at AD/PD in April 2020 where it will mark a significant landmark in the Oryzon/ADDF journey.

Ihab Hajjar, MD—Emory University

Ihab Hajjar, MD, is an internist and a geriatrician in the Emory University Department of Medicine, Division of General Medicine and Geriatrics. Dr. Hajjar completed his MD at the American University of Beirut and his internal medicine residency at the Cleveland Clinic Foundation. He also completed a two-year fellowship in geriatrics at the Medical College of Wisconsin. After completing his training, he served on the faculty at University of South Carolina until 2006. He then moved to Harvard Medical School, where he was an assistant professor of medicine and associate director of the CV Research Lab. He moved to the University of Southern California in 2011, and then to Emory in 2013.

His research is focused on the link between hypertension and vascular disease with brain health including cognitive performance, cerebrovascular function. In particular, he is studying the effects of antihypertensive medications that modulate the renin angiotensin system on both prevention of cognitive decline and as potential therapeutic modalities for early dementia.
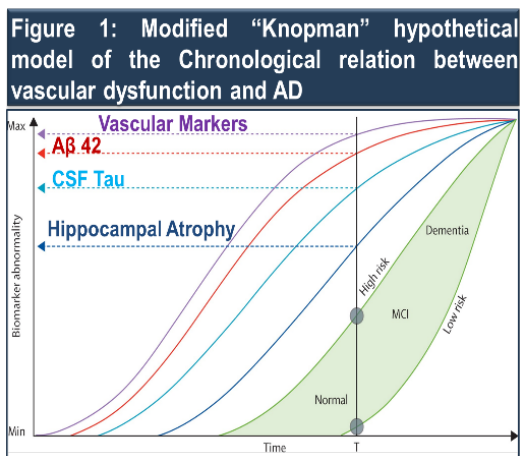
Dr. Hajjar has published more than 50 scientific articles and book chapters and has been funded by grants from National Institute of Health and other governmental and private organizations since 2001. Dr. Hajjar sees patients with cognitive disorders and/or vascular risk factors at the Memory Disorder Clinic at the Emory clinic and is the medical director of the Integrated Memory Care Clinic (IMCC) at Emory.

Vascular Approaches for Alzheimer's Treatment

Ihab Hajjar

Emory University

Evidence continues to accumulate that vascular changes may be early "triggers" that lead to the initiation/propagation of hypoperfusion, amyloidosis and neurodegeneration (Fig 1). Our prior work suggests that systemic and cerebral vascular dysfunction contributes to cognitive impairments in normal adults and APOE4 carriers, and that molecular/cellular modulators of vascular function (oxidative stress (OS), renin angiotensin aldosterone system (RAAS), endothelial activity and vascular regeneration) are related to cognitive and neuropathological indicators of AD. Multiple recent trials have shown that lowering CV risk is linked to lower risk of future cognitive decline and dementia. This opens an untapped pool of potential targets that might be effective in managing the symptoms or pathogenesis of AD and vascular cognitive impairment (VCI). My work has focused on angiotensin receptor blockers, due to their pleiotropic effects. I will present a summary of the past and current work including observational studies and clinical trials including 2 recently completed trials in transgenic AD rats and in MCI with hypertension. I will also provide a summary of our ongoing trial in non-hypertensive prodromal AD.

Figure 1: Modified "Knopman" hypothetical model of the Chronological relation between vascular dysfunction and AD

SESSION IV: NOVEL BIOMARKER APPROACHES
Chair: Nicole Bjorklund, PhD—Alzheimer's Drug Discovery Foundation

Nicole Bjorklund, PhD, manages the Diagnostics Accelerator Initiative working closely with ADDF's partners at Gates Ventures. In this capacity, she proactively engages promising biomarker programs and supports the development of these biomarkers for use in clinical practice for Alzheimer's disease and related dementias. She also supports the management of ADDF's core Request for Proposals by providing scientific review of biomarker proposals and tracking program progress.

Dr. Bjorklund came to the ADDF from Albert Einstein College of Medicine where she was an Assistant Research Professor and Operations Director of the Biomarker and Biorepository core facilities. Her laboratories, as part of the CTSA-supported Institute of Clinical and Translational Research, supported clinical research studies at Einstein and Montefiore Medical Center. She remains an adjunct faculty member at Einstein.

Dr. Bjorklund completed postdoctoral training at University of Texas Medical Branch, where she investigated molecular resistance mechanisms to Alzheimer's disease. She earned a doctorate in biochemistry at Washington State University and a bachelor's degree in chemistry from Boise State University. Dr. Bjorklund has authored numerous peer-reviewed publications and is a member of the Society for Neuroscience and New York Academy of Sciences.

FDG PET, Tau PET, and MR Imaging Biomarkers in Alzheimer's Disease Therapeutic Trials
Dawn Matthews, MS, MBA—ADMdx

Resilience Biomarker NPTX2 and AD Progression
Paul Worley, MD—Johns Hopkins University

The Utility of cFLIP and MCL I and their Regulatory MicroRNAs as Novel Biomarkers of Alzheimer's Disease
Esmerina Tili, PhD—OSU/Gnome Diagnostics, LLC

Ocular Approaches for Alzheimer's Diagnosis
Swati More, PhD—University of Minnesota

Dawn Matthews, MS, MBA—ADMdx

Dawn Matthews, MS, MBA, is Chief Executive Officer of ADM Diagnostics (ADMdx) and leads the development of image analysis technology to support the diagnosis of brain disorders and detection of treatment effects. Under her direction, ADMdx has developed analysis products to support the differentiation of Alzheimer's disease and other dementias, and to aid in clinical trials.

Ms. Matthews has led image analysis for studies including the evaluation of rasagiline in mild to moderate Alzheimer's disease patients, a multi-modality study of at-risk patients with Down syndrome, and studies of imaging biomarkers in dementias, Parkinson's disease, and traumatic brain injury. She has co-authored and directed multiple grants from the National Science Foundation and the National Institutes of Aging focused on innovative brain image analysis tools.

Ms. Matthews is co-chair of the Radiologic Society of North America Quantitative Imaging Biomarker Alliance (QIBA) Amyloid Profile working group, and previously served as Imaging Biomarker co-chair for the Critical Path for Parkinson's Consortium. She has been a regular speaker at Alzheimer's conferences, and is a co-author of book chapters and publications related to imaging biomarker advances in the dementia field.

Prior to her work in neuroimaging, she was a Director of Business Development at Motorola Biochip Systems, Vice President and co-founder of Aksys Ltd, a medical device company, and a senior principal engineer at Baxter Healthcare. Ms. Matthews holds a Master of Science degree in Electrical Engineering with biomedical emphasis from the University of Michigan, a Master of Business Administration from Northwestern University, and a Bachelor of Science in Electrical Engineering from the University of Notre Dame.

FDG PET, Tau PET, and MR Imaging Biomarkers in Alzheimer's Disease Therapeutic Trials

Dawn Matthews

ADMdx

The need for effective therapeutics to treat and/or prevent Alzheimer's disease (AD) remains urgent. Yet, the majority of late stage, pivotal clinical trials have failed to meet their target endpoints after enrolling many patients and incurring tremendous cost in resources and time. Among clinical trial challenges, detection of treatment effect has been impeded by inclusion of patients without the target disease, high variability in disease severity and rates of clinical worsening, and variability of clinical endpoints. The use of imaging biomarkers in therapeutic clinical trials can help to address these confounds by aiding in patient selection, stratification, and detection of therapeutic effect on brain function and pathology.

The measurement of amyloid using PET (positron emission tomography) imaging, cerebrospinal fluid (CSF), or other emerging methods can confirm the presence of one of the two hallmark pathologies associated with AD. Confirmation of amyloid can prevent inclusion of patients with certain dementias other than AD. Disease progression and clinical trajectory, however, correlate most strongly with neuronal activity, neurodegeneration, and tau burden. These can be measured using FDG PET, volumetric MRI, and tau PET, respectively. FDG PET can also provide a sensitive measure of neuronal response to treatment, whether symptomatic or associated with disease modification. In addition, these modalities can also inform regarding the likelihood of amyloid positivity. The use of FDG PET, tau PET, and volumetric MRI, their relationships to one another, and their correlation with clinical endpoints have been illustrated in data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and in a Proof of Concept (POC) Phase II clinical trial of rasagiline in patients with AD. Findings will be presented along with a discussion of the impact of image analysis methods, and the potential to accelerate treatment feasibility studies.

Paul Worley, MD—Johns Hopkins University

Paul Worley, MD, is a professor of neuroscience at the Johns Hopkins University School of Medicine. An expert in the molecular basis of specific forms of long-term learning and memory, Dr. Worley serves on the faculty of the Institute for Basic Biomedical Sciences and as an associated investigator with the Alzheimer's Disease Research Center.

Dr. Worley's laboratory focuses on a class of proteins found at the interfaces of connecting neurons (synapses) that ramp up as the neurons engage in information processing and storage. These proteins directly modify the strength of the signals sent between neurons and are essential for information storage.

Recent work reveals how molecules that regulate reward-signaling neuronal responses (such as dopamine) can selectively strengthen communication across synapses – and implicates this process in addiction.

Dr. Worley's research also has clinical potential in the treatment of patients with degenerative memory conditions such as Alzheimer's disease.

Resilience Biomarker NPTX2 and AD Progression

Paul Worley

Johns Hopkins University

Memory consolidation requires rapid, de novo synthesis of cellular immediate early genes (IEGs) that function at excitatory synapses. The IEG NPTX2 is expressed by pyramidal neurons and normally functions to enhance excitatory drive of parvalbumin (PV) interneurons thereby acting to homeostatically balance inhibition and excitation in cortical and hippocampal circuits (1). In human AD neocortex NPTX2 mRNA and protein are prominently reduced relative to other synaptic proteins (2). NPTX2 loss of function (LOF) is confirmed in human AD brain by coordinate down-regulation of a "secondary" biomarker GluA4, which is essential for PV interneuron function and is known from mouse studies to be down-regulated consequent to combined Aß amyloidosis and NPTX2 LOF (2). The NPTX2-GluA4 parameter is also down-regulated in normative aging, though to a lesser degree than in AD (2). Consistent with its extracellular site of action, NPTX2 is present in human CSF where levels distinguish AD or mild cognitive impairment (MCI) from age-matched controls (2). NPTX2 enhances the diagnostic performance of Tau/pTau and correlates with both cognitive measures and hippocampal volume (2). In cognitively normal older individuals, CSF NPTX2 correlates with fMRI measures of functional connectivity in the salience network (3). In individuals with MCI/early AD, CSF Tau/NPTX2 correlates with disease progression and outperforms other excitatory synaptic markers (4). We propose that NPTX2 acts as a resilience mechanism that maintains excitatory homeostasis as part of the memory consolidation process. NPTX2 LOF disrupts memory consolidation and shifts the burden of homeostasis onto alternative homeostatic mechanisms that weaken synapses and generate Aß. Hence, processing of new information creates an aberrant homeostatic response that drives synapse loss and reduced functional connectivity in aging and disease progression in MCI/AD.

Esmerina Tili, PhD—OSU/Gnome Diagnostics, LLC

Esmerina Tili, PhD, currently at the Ohio State University, holds a PhD on Genetics from Thomas Jefferson University, Philadelphia. A significant part of Dr. Tili's scientific work is dedicated toward understanding of the molecular malfunctions leading to prolonged chronic inflammation particularly neuroinflammation and ultimately resulting in neurodegeneration.

Since 2007, when she discovered that miR-155 is a pro-inflammatory microRNA, acting downstream of LPS/TLR signaling in macrophages she has been using different mouse models of miR-155 to understand the effects of this gene in neuroinflammation and ischemic spinal cord injury, Down's syndrome dementia, and other neuro-related pathologies. Part of Dr. Tili's work is funded by NIH and she is a highly cited scientist.

The Utility of cFLIP and MCL I and their Regulatory MicroRNAs as Novel Biomarkers of Alzheimer's Disease

Esmerina Tili

OSU/Gnome Diagnostics, LLC

Alzheimer's disease shows marked heterogeneity in the distribution of hyperphosphorylated tau protein in a given brain section. This point was exploited to divide thin frozen brain tissues from the cortex and hippocampus from people with Alzheimer's disease into hyperphosphorylated tau protein positive and negative by doing immunohistochemistry for the abnormal protein on subjacent sections. qRTPCR for a large variety of potential biomarkers identified mRNAs associated with apoptosis (inhibitors and facilitators) and nuclear transport as significantly increased in the Alzheimer's disease brain tissues with hyperphosphorylated tau protein versus those hyperphosphorylated tau protein negative or normal controls. Immunohistochemistry for the corresponding proteins with co-expression analysis confirmed that many bcl2 family members (bclx, bcl2, Mcl1, BAX, BAD, BIM), cFLIP, and importin-β/exportin-5 were up-regulated in the Alzheimer's disease brains and co-expressed with hyperphosphorylated tau protein. The data suggests that neurons with neurofibrillary tangles may be viable albeit dysfunctional and that the abnormal expression of several proteins involved in cell turnover may be preventing normal neuronal turnover and, thus, may serve as novel biomarkers of the disease and potential targets for treatment.

Swati More, PhD—University of Minnesota

Swati More, PhD, received her doctorate in Medicinal Chemistry from the University of Minnesota and acquired postdoctoral training in pharmacokinetics and pharmacogenomics at the University of California, San Francisco.

Dr. More was appointed to the faculty of the Center for Drug Design in 2013. Research in her laboratory seeks to identify, describe and solve biological problems through chemical means. A keen emphasis is placed on mechanistic probes into neurodegeneration, with diagnostic tools and therapeutic agents being the end-goals.

Dr. More in collaboration with Prof. Robert Vince at the Center for Drug Design, has developed a retinal hyperspectral imaging technique that has shown promise as an early diagnostic tool for Alzheimer's disease. This technology has recently been licensed to RetiSpec, a medical device company focused on Alzheimer's detection, with the hope that it will be developed into a product approved for use by the public.

Ocular Approaches for Alzheimer's Diagnosis

Swati More

University of Minnesota

Alzheimer's disease (AD) is the leading cause of dementia, with 5.4 million affected in the US and an estimated 14 million expected by 2050. It is well known that damage to the brain from AD occurs years before patients become symptomatic. Attempted therapies have been unsuccessful largely because they have targeted patients with clinical signs of AD who have already suffered irreversible damage. Therefore, a noninvasive tool to detect patients destined to develop AD is one of the holy grails of research in this field. The retina is a developmental extension of the brain and has been proposed as a window to evaluate changes in AD. We attempted to use retinal spectral characteristics as biomarkers to identify patients with preclinical and symptomatic AD, facilitating therapeutic interventions before irreversible memory loss. Initial experiments with hyperspectral imaging (HSI) offered a similar pattern of spectral variation with respect to wavelength in post-mortem human brain and retina samples, highlighting similar pathological and hence spectral changes in these tissues. The follow up studies in a transgenic AD mouse model demonstrated ability of the retinal HSI technique to visualize Alzheimer's related retinal changes before confirmed cognitive decline in these mice. The method was later translated into humans and demonstrated the ability to visualize early AD-related retinal changes. Reduced spectral amplitudes observed in human and mice retina at shorter wavelengths compared to controls correlated with the levels of soluble amyloid (Aβ) aggregates, which are thought to be the precursor to Aβ plaques. The underlying principle is Rayleigh light-scatter, which is expected from Aβ aggregates of particle sizes present in early pathology. The amyloid spectral signature observed is unaffected by eye pathologies such as glaucoma, and cataract. The retinal HSI technique shows promise for detection of preclinical AD; it is conducted in a truly non-invasive manner, without application of an exogenous label, and thus potentially suitable for population screening.

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From developing new therapies that treat and prevent disease to helping people in need, we're committed to improving health and well-being around the world. Our vision is to make a difference in the lives of people globally through our innovative medicines, vaccines, biologic therapies, consumer care and animal health products. We aspire to be the best healthcare company in the world and are dedicated to providing leading innovations and solutions for tomorrow.

Alzheimer's
Drug Discovery
Foundation

www.alzdiscovery.org