

9th International Conference on Alzheimer's Disease Drug Discovery

New York, NY • October 6-7, 2008

Presented by the Alzheimer's Drug Discovery Foundation



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WELCOME



On behalf of the Alzheimer's Drug Discovery Foundation (ADDF), I am pleased to welcome you to the 9th International Conference on Alzheimer's Disease Drug Discovery in New York.

This event brings together academic and industry scientists with an intended target of accelerating the development of novel drug discovery programs for Alzheimer's disease. The two-day agenda spanning over four ample sessions will offer updates on ongoing research as well as highlight new studies and concepts.

The three-dimensional aim of the meeting links discussions on scientific progress on drug discovery programs aimed at Alzheimer's disease with networking opportunities for scientists to share information and resources, and finally, the publication and distribution of a post-meeting report in a peer-reviewed scientific journal.

I am pleased to see the strong encouragement of participation by students. They are critical to the future of our field and I sincerely hope they take advantage of this excellent opportunity to interact directly with the experts in their field.

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

As this is an annual event for our Foundation, we hope you will use the attached survey to provide us with your feedback and help us plan an event better conference for 2009!

My hope is that all participants will leave this conference with new inspirations and new prospects for future collaborations. Once again, welcome to the 9th International Conference on Alzheimer's Disease Drug Discovery!

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

MISSION

The Alzheimer's Drug Discovery Foundation (ADDF) is the **only** public charity whose sole mission is to rapidly accelerate the discovery and development of drugs to prevent, treat and cure Alzheimer's disease (AD).

We raise and award funds to academic and biotechnology scientists conducting drug discovery research for AD.

We use a **venture philanthropy** model to bridge the worldwide funding gap between basic research and later-stage development, using any return on investment to support new research programs.

ABOUT US

As a public charity, ADDF partners with individuals, corporations, foundations and government agencies to advance drug discovery for Alzheimer's disease.

ADDF is affiliated with the Institute for the Study of Aging (ISOA), a private foundation created by the Lauder family in 1998. ISOA serves as a scientific, financial and business development resource for ADDF, enabling 90% of funds raised by ADDF to be used directly for research.

A TRACK RECORD OF SUCCESS

ISOA and ADDF have a track record of identifying and supporting excellent AD drug discovery programs. To date, we have awarded **\$28.7M** for **195** research programs and conferences in **12** countries.

Our **Academic Drug Discovery Program** has provided **\$22.5M** to **148** scientists. They have created entirely new classes of drugs in development for AD, screened millions of compounds, identified hundreds of leads, executed many patents and licenses, and are approaching or entering clinical trials with several new drugs.

Through our **Biotechnology Programs**, we have invested **\$5.2M** in **22** biotechnology companies worldwide. Eleven have received follow-on funding commitments of over **\$325M**.

Our **Biotechnology Founders Program** assists in the founding of new companies dedicated to AD drug discovery. Two companies, Allon Therapeutics (NPC:TSX) and Zapaq, Inc. have been supported to date. Established as a pre-clinical, private company, Allon is now publicly traded, in human clinical trials for AD, and recently voted one of the 10 best biotech companies in Canada. Zapaq has become a leader in developing beta-secretase inhibitors for AD, a key therapeutic target, is now managed and financed by a prominent venture capital group, and will enter clinical trials in the near future.

Our **Biotechnology Development Program** assists existing early-stage companies in pursuing AD drug discovery. For example, of **128** initial public offerings (IPOs) in biotechnology from 1998 to 2004, only 5 companies reported AD therapeutic programs. The only company with an AD clinical trial at the time of IPO was Corcept Therapeutics, and that trial was funded by ISOA. Another success is Acumen Pharmaceuticals, which received a **\$133,493** grant in January, 2003, and executed a **\$48M** licensing deal with Merck in February of 2004.

SPEAKERS

Ottavio Arancio, MD, PhD, Columbia University

Ben Bahr, PhD, University of Connecticut

Randall Bateman, MD, Washington School of Medicine

Michelle Block, PhD, Virginia Commonwealth University

Roberta Brinton, PhD, University of Southern California

John Cashman, PhD, Human Biomolecular Research Institute

Gabriela Chiosis, PhD, Memorial Sloan-Kettering Cancer Institute

A. Claudio Cuello, MDsc, FRSC, McGill University

Douglas Feinstein, PhD, University of Illinois

Howard Fillit, MD, Alzheimer's Drug Discovery Foundation

S. Prasad Gabbita, PhD, P2D Biosciences

Illana Gozes, PhD, Tel Aviv University and Allon Therapeutics, Inc.

Varghese John, PhD, Buck Institute

Anthony Koleske, PhD, Yale University

Alan Kozikowski, PhD, University of Illinois at Chicago

Jeff Kuret, PhD, Ohio University

Thomas Lanz, Pfizer, Inc.

Daniel Laskowitz, MD, MHS, Duke University Medical Center

Frank Longo, MD, PhD, Stanford University

Eva-Maria Mandelkow, PhD, Max Planck Unit for Structural Biology

Karoly Nikolich, PhD, Stanford University and Amnestix, Inc.

Juan Sanchez-Ramos, MD, PhD, University of South Florida

Horacio Uri Saragovi, PhD, Lady Davis Institute for Medical Research

Hyman Schipper, MD, PhD, FRCPC, McGill University and Osta Biotechnologies

Diana Shineman, PhD, Alzheimer's Drug Discovery Foundation

Einar Sigurdsson, PhD, New York University Medical Center

David Vocadlo, PhD, Simon Fraser University

D. Martin Watterson, PhD, Northwestern University

Karl H. Weisgraber, PhD, Gladstone Institute of Neurological Disease

Moussa B.H. Youdim, PhD, Technion-Israel Institute of Technology

PROGRAM

Monday, October 6, 2008	
7:45 – 8:30 am	Registration & Continental Breakfast
8:30 – 8:35	Welcome & Opening Remarks - Howard Fillit, MD, Executive Director, Alzheimer's Drug Discovery Foundation
8:35 – 8:55	Plenary Talk: Neurobiology of Memory and Learning: Implications for Alzheimer's Disease and Cognitive Aging - Ottavio Arancio, MD, PhD, Columbia University
I. Neuroprotection— Chair: Frank Longo, MD, PhD, Stanford University and Pharmatrophix	
8:55–9:00	Session Overview – Frank Longo, MD, PhD
9:00–9:20	Development of p75 Neurotrophin Receptor Small Molecule Ligands for Alzheimer's Therapy—Frank Longo, PhD
9:20–9:30	Q&A
9:30–9:50	Validation of Trk (and p75) Receptors as Therapeutic Targets in Neurodegenerative Disorders - Horacio Uri Saragovi, PhD, Lady Davis Institute for Medical Research
9:50–10:00	Q&A
10:00–10:20	Screening for Alzheimer Therapeutics Based on a Novel Target - Varghese John, PhD, Buck Institute
10:20–10:30	Q&A
10:30–10:50	Does Inhibition of Rho Signaling Protect Against Synapse Loss and Dendritic Regression in Alzheimer's Disease Mouse Models? - Anthony Koleske, PhD, Yale University
10:50–11:00	Q&A
11:00–11:10	BREAK
11:10–11:30	Updates on AL-108: Case Study for Drug Discovery and Development toward Cognitive Enhancement and Neuroprotection - Illana Gozes, PhD, Tel Aviv University and Allon Therapeutics, Inc.
11:30–11:40	Q&A
11:40am–12:00pm	Chromatin Remodelers for Recovery of Learning and Memory - Alan Kozikowski, PhD, University of Illinois at Chicago
12:00–12:10	Q&A
12:10–12:30	G-CSF Reduces Brain Amyloid, Increases Expression of Synaptophysin and Improves Cognition in a Mouse Model of AD— Juan Sanchez-Ramos, MD, PhD, University of South Florida
12:30–12:40	Q&A
12:40–1:05	Allopregnanolone Regulation of Neurogenesis, Alzheimer's Pathology Burden and Cognition in the Aging Male Triple Transgenic Mouse Model of Alzheimer's Disease - Roberta Brinton, PhD, University of Southern California
1:05–1:15	Q&A
1:15–2:15	LUNCH
II. Anti-Amyloid & Misfolding— Chair: Diana Shineman, PhD, Alzheimer's Drug Discovery Foundation	
2:15–2:20	Session Overview – Diana Shineman, PhD, Alzheimer's Drug Discovery Foundation
2:20–2:40	Anti-amyloidogenic Effects of Noradrenaline and PPARdelta Agonists - Douglas Feinstein, PhD, University of Illinois
2:40–2:50	Q&A
2:50–3:10	Validation and Optimization of Stable Isotope Labeling Kinetic Analysis of Amyloid Beta from Human Cerebrospinal Fluid - Randall Bateman, MD, Washington University School of Medicine and C2N Diagnostics
3:10–3:20	Q&A
3:20–3:40	Immune Defects in Alzheimer's Disease: New Medications Development - John Cashman, PhD, Human Biomolecular Research Institute
3:40–3:50	Q&A
3:50–4:00	BREAK
4:00–4:20	Understanding the Structural Basis for the Association of ApoE4 with Alzheimer's Disease: Opening the Door for Therapeutic Approaches - Karl H. Weisgraber, PhD, Gladstone Institute of Neurological Disease
4:20–4:30	Q&A
4:30–4:50	A Novel Combined Experimental Therapy in an Alzheimer's Transgenic Model - A. Claudio Cuellar, MD, DSc, FRSC, McGill University
4:50–5:00	Q&A
5:00–5:20	Development of Hsp90 Inhibitors as Novel Therapies for AD - Gabriela Chiosis, PhD, Memorial Sloan-Kettering Cancer Ctr
5:20–5:30	Q&A
5:30–5:50	ApoE Therapeutics - Daniel Laskowitz, MD, MHS, Duke University
5:50–6:00	Q&A
6:00–6:05	Closing Remarks - Diana Shineman, PhD, Alzheimer's Drug Discovery Foundation
6:05–7:30	NETWORKING RECEPTION

Tuesday, October 7, 2008

8:00 – 8:30 am	Continental Breakfast
8:30 – 8:50	Phosphodiesterases and Synaptic Plasticity: Novel Approaches to the Treatment of Alzheimer's Disease - Thomas Lanz, Pfizer
III. Anti-Tangles & Frontotemporal Dementia—Chair: Jeffrey Kuret, PhD - Ohio State University	
8:50 – 8:55	Session Overview – Jeffrey Kuret, PhD
8:55 – 9:15	Selective Inhibitors for O-glycosylation Processing Enzymes: Design, Synthesis, and Effects on Tau Phosphorylation <i>in vivo</i> - David Vocadlo, PhD, Simon Fraser University
9:15 – 9:25	Q&A
9:25 – 9:45	Testing of New Lysosomal Modulatory Drugs for Reducing Tau Aggregates and Other AD-Related Changes - Ben Bahr, PhD, University of Connecticut
9:45 – 9:55	Q&A
9:55 – 10:15	Tau Aggregate Inhibitors: a Medicinal Chemistry Point of View - Jeff Kuret, PhD, Ohio State University
10:15 – 10:25	Q&A
10:25 – 10:45	Tau-Focused Vaccine Therapy for Alzheimer's Disease and Related Tauopathies - Einar Sigurdsson, PhD, New York University Medical Center
10:45 – 10:55	Q&A
10:55 – 11:05	BREAK
11:05 – 11:25	MARK as a Target for Neurodegenerative Disease - Eva-Maria Mandelkow, MD, PhD, Max-Planck Unit for Structural Molecular Biology
11:25 – 11:35	Q&A
IV. Anti-inflammatory & Anti-oxidant Strategies—Chair: D. Martin Watterson, PhD, Northwestern University	
11:35 – 11:40	Session Overview – D. Martin Watterson, PhD
11:40 am – 12:00 pm	Suppression of Glial HO-1 Activity as a Potential Neurotherapeutic Intervention in AD - Hyman Schipper, MD, PhD, FRCPC, McGill University and Osta Biotechnologies Inc.
12:00 – 12:10	Q&A
12:10 – 12:30 pm	Gene-Regulating Protein Kinase Inhibitors as Potential Alzheimer's Disease Therapeutics - D. Martin Watterson, PhD, Northwestern University
12:30 – 12:40	Q&A
12:40 – 1:40	LUNCH
1:40 – 2:00	NADPH Oxidase as a Therapeutic Target in Alzheimer's Disease - Michelle Block, PhD, Virginia Commonwealth University
2:00 – 2:10	Q&A
2:10 – 2:30	KIBRA as a Novel Target for Alzheimer's Disease - Karoly Nikolich, PhD, Stanford University and Amnestix, Inc.
2:30 – 2:40	Q&A
2:40 – 3:00	Small Molecule TNF-Alpha Inhibitors for Alzheimer's Disease - S. Prasad Gabbita, PhD, P2D Biosciences
3:00 – 3:10	Q&A
3:10 – 3:30	Novel Therapeutic Approaches Constituting Multimodal Drugs for Alzheimer's Disease - Moussa B.H. Youdim, PhD, Technion-Israel Institute of Technology
3:30 – 3:40	Q&A
3:40 – 3:50	Closing Remarks - Howard Fillit, MD, Alzheimer's Drug Discovery Foundation

ADDF YOUNG INVESTIGATOR SCHOLARSHIP RECIPIENTS

Congratulations to the winners of the 2008 **ADDF Young Investigator Scholarships!** These highly prestigious Scholarships recognize the early achievements of talented young investigators and seek to encourage the further career development of the next generation of research scientists. In addition to individual recognition, the Scholarships honor the organizations responsible for creating and preserving an environment conducive to profound research accomplishment.

Brian Couch	Yale University, Department of Molecular Biophysics and Biochemistry
Yitshak Francis	Institute of Child Health, UCL (London), Department of Molecular Biology
Srinath Kasturirangan	Arizona State University, Department of Bioengineering
Tao Ma	Weill Cornell Medical College of Cornell University, Department of Neurology
Karla Malloy	University of California San Diego School of Medicine
Boobalan Pachaiyappan	University of Illinois at Chicago, Medicinal Chemistry
Lisa Placanica	Cornell Weill Medical College / Memorial Sloan Kettering
Christopher Chad Shelton	Cornell Weill Graduate School of Medical Sciences
Sharotka Simon	Brandeis University, Massachusetts
Xingiong Wang	Case Western Reserve University, Department of Pathology

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

Alzheimer's Drug Discovery Foundation expresses its gratitude to the following supporters of this medical education event:

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Howard Fillit, MD, Alzheimer's Drug Discovery Foundation

Dr. Fillit, a geriatrician and neuroscientist, is the founding Executive Director of the Institute for the Study of Aging, Inc. as well as its affiliated public charity the Alzheimer's Drug Discovery Foundation, both of which are dedicated to funding drug discovery for Alzheimer's disease. Dr. Fillit was formally the Corporate Medical Director for Medicare at NYLCare Health Plans (now a division of Aetna, Inc.), where he was responsible for over 125,000 Medicare members in 8 regional markets. He has also had a distinguished academic career at The Rockefeller University and The Mount Sinai Medical Center (NY), where he is currently a clinical professor of geriatrics and medicine and a professor of neurobiology. Dr. Fillit has received many awards and honors, including the Rita Hayworth Award for Lifetime Achievement from the Alzheimer's Association. He is a fellow of the American Geriatrics Society, the American College of Physicians, the Gerontological Society of America, and the New York Academy of Medicine. Dr. Fillit is the author or co-author of more than 250 publications, including the leading international Textbook of Geriatric Medicine and Gerontology. He served as a consultant to a variety of individuals, managed care organizations, health care systems, and pharmaceutical and biotechnology companies.



Diana Shineman, PhD, Alzheimer's Drug Discovery Foundation

Diana Shineman, PhD is the Assistant Director for Scientific Affairs at the Alzheimer's Drug Discovery Foundation, where she is responsible for developing and managing all aspects of the Foundation's drug discovery research programs.

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

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



Ottavio Arancio, MD, PhD, Columbia University

Dr. Ottavio Arancio received his PhD and MD from the University of Pisa (Italy). From 1981 to 1986 he took residency training in Neurology at the University of Verona (Italy). Dr. Arancio has held Faculty appointments at Columbia University, NYU School of Medicine and at SUNY HSCB. In 2004 he became Faculty member of the Department of Pathology and Taub Institute for Research on Alzheimer's Disease and the Aging Brain at Columbia University. His honors include the "G. Moruzzi Fellowship" (Georgetown University), the "Anna Villa Rusconi Foundation Prize" (Italy), and the "INSERM Poste vert Fellowship" (France), Fidia Fellowship, Italy; Speaker's Fund for Biomedical Research Award; Investigator Initiated Research Award from the Alzheimer

Association; AHAF centennial Award, Zenith Award, and Margaret Cahn Research Award (2008). Dr. Arancio is a cellular neurobiologist who has contributed to the characterization of the mechanisms of learning in both normal conditions and during neurodegenerative diseases. During the last ten years he has pioneered the field of mechanisms of synaptic dysfunction in Alzheimer's disease. Dr. Arancio's laboratory has focused primarily on events triggered by amyloid protein. These studies, which have suggested new links between synaptic dysfunction and amyloid protein, are of a general relevance to the field of Alzheimer's disease both for understanding the etiopathogenesis of the disease and for developing therapies aiming to improve the cognitive symptoms.

Neurobiology of Memory and Learning: Implications for Alzheimer's Disease and Cognitive Aging

Ottavio Arancio
Columbia University

The ability to acquire new ideas from experience and to store these ideas in memory is a fascinating and distinctive feature of our mental life. However, when learning and memory processes are impaired, disorders ranging from the inconvenient benign forgetfulness associated with normal aging to the devastating memory losses associated with Alzheimer disease arise. During the last 50 years, researchers have unveiled many of the mechanisms underlying the cellular and molecular bases of learning and memory. These studies have opened the possibility of clarifying how memory processes are impaired in disease states. From these new avenues of research, an increasing number of new targets will become available for drug discovery in the near future.



Ben Bahr, PhD, University of Connecticut

Upon receiving his PhD at University of California-Santa Barbara, Ben Bahr joined the large research team at the Center for the Neurobiology of Learning and Memory at University of California-Irvine. He then moved on as Research Scientist and patent advisor for Cortex Pharmaceuticals working on memory enhancing drugs before joining the faculty at the University of Connecticut in 1997. Dr. Bahr has appointments in the Department of Pharmaceutical Sciences and the Department of Physiology and Neurobiology, and he is an active member of the Neurosciences Program as well as Northeastern University's Center for Drug Discovery. His laboratory combines molecular, cellular, and behavioral experiments to understand pathogenic cascades that cause synaptic and cognitive dysfunction, and studies new protection strategies in models of Alzheimer's disease and excitotoxicity. He has over 100 publications and is the primary founder of Synaptic Dynamics, Inc. that is developing first-in-class drugs for Alzheimer's and other diseases.

Testing New Lysosomal Modulatory Drugs for Reducing Protein Aggregates and Other AD-Related Changes

Ben A. Bahr
University of Connecticut

Accumulation of un-degraded substrates leads to CNS effects in Alzheimer's disease (AD), frontotemporal dementia, other age-related neurodegenerative disorders, and lysosomal storage diseases (LSDs). The pathogenic accumulations result in several clinical manifestations including progressive cognitive deficits. Efficient clearance of aggregation-prone oligomeric species is essential to reduce protein accumulation stress and the associated synaptic compromise that is widely believed to be the best correlate of cognitive decline in many types of dementia. A cultured hippocampal slice model of protein accumulation was used to study synaptic effects and plausible strategies to promote protein clearance and synaptic protection. The model system identified a cascade leading from induced intracellular deposits to loss of microtubule integrity, transport failure, and gradual reductions of synaptic markers. This synaptopathogenic cascade was linked to hyperphosphorylated tau and neurofibrillary degeneration, and is likely responsible for loss of synapses and cognitive ability in several dementias. The lysosomal modulator Z-Phe-Ala-diazomethylketone (PADK) was found to greatly enhance compensatory lysosomal activation that occurs in response to protein accumulation stress in the slice model and in human diseases. PADK reduced PHF-tau aggregates as well as amyloidogenic species in the hippocampal slices, and, correspondingly, restored microtubule stability, transport processes, and synaptic integrity. The slice model is being used to characterize lysosomal modulators and to identify potentially disease modifying lead compounds among derivatives of PADK and first-generation peptidomimetics. Modulator treatment *in vivo* resulted in 2- to 8-fold increases in cathepsins, the major family of protein clearance enzymes in lysosomes, without any indications of synaptic pathology, ultrastructural changes, behavioral abnormalities, or major organ malfunction. Mouse models of AD are also being used to assess drug effects on protein clearance, synaptic protection, and improvement of behavioral deficits. As in previous studies, lysosomal modulation is implicated as a potential strategy against tau-related pathology and other AD-type deposits, and the slice model is proving to be valuable for developing the first-in-class drugs as an effective treatment for protein accumulation disorders.



Randall Bateman, MD, Washington University School of Medicine

Dr. Bateman attended Washington University where he received a BS degree in Biology (1995) and a BS degree in Electrical Engineering (1995). He attended Case Western Reserve University School of Medicine where he received his M.D. (2000) with special emphasis on the neurosciences. He completed a medical internship (2001) at Barnes-Jewish Hospital followed by Neurology residency (2004) at Washington University in St. Louis. He then completed post-doctoral research training with David M. Holtzman, M.D. as mentor and clinical research fellowship training at the Washington University ADRC with John Morris, MD as mentor. Dr. Bateman treats patients with dementia at the Memory Diagnostic Center of Washington University. He is the recipient of multiple grants and awards from the NIH and outside agencies. He has received awards for his research including the AAN Foundation Corporate Roundtable Clinical Research Fellowship (2004), an American Neurological Association Plenary Session Speaker (2005), a World Technology Award Nominee for Health and Medicine Associate (2006), Scientific American 50, award for outstanding technological leadership, chosen as one of the top 50 scientific advancements of 2006, and the Kopolow Award (2007).

Validation and Optimization of Stable Isotope Labeling Kinetic Analysis of Amyloid Beta from Human Cerebrospinal Fluid

Randall Bateman, MD
Washington University School of Medicine

The amyloid hypothesis suggests that amyloid-beta ($A\beta$) plays a critical role in the pathogenesis of Alzheimer's disease (AD). This hypothesis proposes that accumulation of $A\beta$, in toxic forms, leads to downstream events that culminate in dementia. To evaluate the physiology of $A\beta$ in humans, we developed a technique to quantify the synthesis and clearance rates of $A\beta$ *in vivo* in humans. In healthy volunteers, $^{13}C_6$ -leucine was administered intravenously to metabolically label $A\beta$ *in vivo*, while serial CSF and blood samples were collected hourly through catheters. $A\beta$ was immunoprecipitated from CSF, the amount of $^{13}C_6$ -leucine incorporated into $A\beta$ was quantified using mass spectrometry, and rates of synthesis and clearance were calculated. The fractional synthesis rate of $A\beta$, as measured in CSF, was approximately 8% per hour, one of the fastest measured production rates of a protein. Demonstrations of the technique will be discussed including the use to study the pathophysiology of $A\beta$ in AD patients compared to controls and also to measure the effects of novel therapeutic agents on $A\beta$ synthesis or clearance.



Michelle Block, PhD, Virginia Commonwealth University

Dr. Block graduated from Iowa State University in 1994 and received her PhD in Genetics from Penn State University in 2002. She then worked as a post doc in the laboratory of Dr. Jau-Shyong Hong at the National Institute of Environmental Health Sciences, the National Institute of Health for 5 years. At present, Dr. Block is an Assistant Professor in the Department of Anatomy and Neurobiology at Virginia Commonwealth University.

Dr. Block's work centers on the role of microglia, the resident innate immune cell in the brain, in neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease. Her research demonstrates that reactive oxygen species (ROS) are critical tools orchestrating microglia-mediated neuron damage. She is currently focusing on identifying the triggers initiating deleterious microglial activation (environmental and endogenous), revealing the mechanisms through which microglial ROS induce neurotoxicity, and applying these findings towards the development of novel therapeutic compounds capable of halting the progression of neurodegenerative disease. Among other awards, Dr. Block is the recipient of the NIH Pathway to Independence Award.

NADPH Oxidase as a Therapeutic Target in Alzheimer's Disease

Michelle L Block

Department of Anatomy and Neurobiology, Virginia Commonwealth University Medical Campus, Richmond, VA 23298

Microglia, the resident innate immune cells in the brain, are strongly implicated in both the pathology and progressive nature of Alzheimer's disease (AD). Microglia are activated in response to both β amyloid ($A\beta$) and neuronal damage, and can become a chronic source of neurotoxic cytokines and reactive oxygen species (ROS). NADPH oxidase is a multi-subunit enzyme complex responsible for the production of both extracellular and intracellular ROS in microglia. Importantly, NADPH oxidase expression is upregulated in AD and is implicated as a key mechanism of microglia-mediated $A\beta$ neurotoxicity. Our research has shown that activation of microglial NADPH oxidase causes neurotoxicity through two mechanisms: 1) extracellular ROS produced by microglia are directly toxic to neurons; 2) intracellular ROS function as a signaling mechanism in microglia to amplify the production of several pro-inflammatory and neurotoxic cytokines. Here, we describe how targeting NADPH oxidase can reduce a broad spectrum of toxic factors (for example, cytokines, ROS, and reactive nitrogen species) to result in inhibition of neuronal damage.



Roberta Brinton, PhD, University of Southern California

Professor Roberta Diaz Brinton is the R. Pete Vanderveen Endowed Chair in Therapeutic Discovery and Development and Professor of Pharmacology and Pharmaceutical Sciences, School of Pharmacy and Biomedical Engineering at the University of Southern California. She is the Director of the USC Science, Technology and Research Program (STAR) science education outreach program. Dr. Brinton is also the Director of the Center for Scientific Translation within the Los Angeles Basin Clinical Translational Science Institute whose partner institutions include the University of Southern California, Childrens Hospital Los Angeles, Kaiser Permanente of Southern California and City of Hope. She earned her Ph.D. in Psychobiology and Neuropharmacology from the University of Arizona as a National Institutes of Health Predoctoral fellow. Dr. Brinton continued her postdoctoral research in Neuroendocrinology at Rockefeller University as a National Institutes of Health postdoctoral fellow and joined the USC faculty in 1988. Awards bestowed on Professor Brinton include Science Educator of the Year by the society for Neuroscience (2006), Woman of the Year (2005, State of California), 10 Best Minds (2005-US News and World Report), and the University of Southern California Remarkable Woman Award (2003).

Allopregnanolone Regulation of Neurogenesis, Alzheimer's Pathology Burden and Cognition in the Aging Male Triple Transgenic Mouse Model of Alzheimer's Disease

Roberta Diaz Brinton, PhD

Department of Pharmacology and Pharmaceutical Sciences, School of Pharmacy and Neuroscience Program, University of Southern California, Los Angeles, CA 90089, USA

Our previous analyses demonstrated that allopregnanolone (AP α) significantly increased proliferation of both rodent and human neural stem cells *in vitro* (Wang et al., 2005). In this study, we investigated 1) the neurogenic efficacy of AP α , to promote *in vivo* neurogenesis in the hippocampal subgranular zone (SGZ) during aging of the male triple transgenic mouse model of Alzheimer's (3xTgAD); 2) the efficacy of AP α to reverse learning and memory deficits of 3xTgAD mice and 3) AP α regulation of Alzheimer pathology. Aging male triple transgenic mice (3xTgAD) were treated with a single injection of AP α (10 mg/kg) and BrdU followed 24 hrs later by an assessment of BrdU incorporation. Results of proliferation analyses demonstrate that a single exposure to AP α (10 mg/kg) significantly increased neurogenesis in the 3 and 6 month old mice while suppressing neurogenesis in the 9 and 12 month old animals. Behaviorally, 3xTgAD male mice exhibited an age associated decline in memory function which was most dysfunctional at 12 and 15 months of age. Following a single exposure, AP α enhanced cognitive performance of the 3, 6 and 9 month old animals whereas it was without effect at 12 and 15 months. A treatment strategy by which AP α could induce both a regenerative response while simultaneously decreasing AD pathology burden was investigated. Male 3xTgAD mice were chronically treated 1/wk for 6 months at 10 mg/kg AP α beginning at one of 2 points; 1) at 3 months of age until 9 months of age or 2) at 6 months of age until 12 months of age. This paradigm was selected to assess the impact of AP α to delay progression of AD pathology prior or subsequent to intraneuronal A β expression. A chronic 1/week exposure to 10 mg/kg AP α for 6 months begun at 3 months of age led to substantial reduction in AD pathology while promoting expression of proteins involved in synapse generation (synaptophysin and spinophilin). AP α was effective in reducing intraneuronal A β following 6 months of once/ week treatment for both 9 and 12 month old animals. Magnitude of reduction was ~ 20% at both ages. Assessment of proliferation is underway. Meanwhile, our preliminary evidence indicates that AP α can increase proteins involved in synapse generation, spinophilin and synaptophysin under the chronic AP α treatment paradigm. Collectively, these findings suggest that the once /week treatment paradigm may be an optimal therapeutic approach for promoting neurogenesis while lowering AD pathology burden.

This research was supported by grants from by the Alzheimer Drug Development Foundation, National Institute on Aging U01AG031115, and the Kenneth T. and Eileen L. Norris Foundation to RDB.



John Cashman, PhD, Human Biomolecular Research Institute

John R. Cashman, PhD, Director and Founder, has more than 23 years experience in biomedical research as a researcher, consultant, entrepreneur or administrator. In 1997, he founded the Human BioMolecular Research Institute, a non-profit research institute dedicated to performing fundamental and applied research to address important human diseases of the central nervous system. Previously, he was Senior Scientist at the Seattle Biomedical Research Institute and prior to that, he was Associate Director for the IGEN Research Institute in Seattle, Washington. In 1984, he was appointed Assistant Professor of Chemistry and Pharmaceutical Chemistry at the University of California, San Francisco. He completed a postdoctoral fellow in the Department of Chemistry at Harvard University in Cambridge, Massachusetts with Professor E.J. Corey (1982-1984). In 1990, Professor Corey received the Nobel Prize. Dr. Cashman received his Masters and doctorate degrees in Medicinal Chemistry from the University of Kansas, Lawrence, Kansas (1982). Prior to graduate school, he obtained bachelor degrees in chemistry and biology at the College of Creative Studies, University of California, Santa Barbara (1977). Dr. Cashman was a University of California Presidents Undergraduate Researcher (1974-1976), received a Sigma Xi Undergraduate Research fellowship (1975), was a PEW Scholar Nominee at the University of California, San Francisco (1986), received a March of Dimes Basil O'Connor Research Award (1986), was appointed Technical Advisor, San Francisco Estuary Project (1990) and was elected Fellow of the American Association for the Advancement of Science in 1996. In 1991, Dr. Cashman was appointed to the Editorial Advisory Board, Chemical Research in Toxicology and in 1999 he was appointed to the Editorial Advisory Board of Current Drug Metabolism. Dr. Cashman is the author of over 155 research articles or book chapters and 6 patents in the area of drug discovery and evaluation.

Immune Defects in Alzheimer's Disease: New Medications Development

John Cashman, Senait Ghirmai, Milan Fiala

Human BioMolecular Research Institute, 5310 Eastgate Mall, San Diego, CA 92121 (www.HBRI.org)

In the past two years, we tested the hypothesis that the innate immune system plays a crucial role in human brain amyloidosis of sporadic AD. Our results suggest that AD amyloidosis may be related to defective brain clearance of A β by monocytes and macrophages. Macrophages of most AD patients do not transport A β into endosomes and lysosomes and AD patients' monocytes do not efficiently clear A β from the brain in vitro and in vivo, although they phagocytize bacteria. In contrast, macrophages of normal subjects transport A β to endosomes and lysosomes and control subjects' monocytes clear A β in AD brain sections. Upon A β stimulation, mononuclear cells of normal subjects up-regulate the transcription of β -1,4-mannosyl-glycoprotein 4- β -N-acetylglucosaminyltransferase (*MGAT3*) and other genes, whereas mononuclear cells of AD patients generally down-regulate these genes. Transcription of Toll-like receptors *TLR1*, *TLR2*, *TLR3*, *TLR5*, *TLR8*, and *TLR10* upon A β stimulation is significantly down-regulated in AD compared to control mononuclear cells. Defective phagocytosis of A β may be related to down-regulation of *MGAT3* and *TLRs*. The natural product curcuminoids have epidemiologic and experimental rationale for use in AD. We reasoned that a pure component would have more activity than the mixture. The curcuminoid compound bisdemethoxycurcumin enhanced defective phagocytosis of A β and up-regulated the transcription of *MGAT3* and *TLR*'s. However, bisdemethoxycurcumin possesses some shortcomings from a pharmaceutical perspective. In the past year we have embarked on a medicinal chemical approach employing Dynamic Medicinal Chemistry to address many of these deficiencies. New, promising compounds have been synthesized to test the hypothesis that correction of innate immune defects in AD patients by curcuminoid products based on bisdemethoxycurcumin may provide novel approaches to AD pathogenesis and therapy.



Gabriela Chiosis, PhD, Memorial Sloan-Kettering Cancer Center

Dr. Gabriela Chiosis is a Principal Investigator in the Program in Molecular Pharmacology and Chemistry at Sloan-Kettering Institute, and an Assistant Attending in the Department of Medicine of Memorial Hospital for Cancer & Allied Diseases, New York. She is also a faculty in several biomedical graduate programs such as the Program in Pharmacology, Weill Graduate School of Medical Sciences, Cornell University, the Tri-Institutional Training Program in Chemical Biology, Sloan-Kettering Institute for Cancer Center, Cornell University and The Rockefeller University and the Cancer Biology Program of the Gerstner Sloan-Kettering Graduate School. She received her graduate training at Columbia University in New York and has joined Memorial Sloan-Kettering Cancer Center in 1998. The Chiosis Laboratory investigates the significance of modulating molecular chaperones in disease treatment. In this respect, it has developed pharmacological tools instrumental in defining the roles of Hsp90 in regulating the stability and function of aberrant protein driving the neurodegenerative phenotype in tauopathies. Hsp90 inhibitors discovered by the lab are the platform for the development of purine-scaffold Hsp90 inhibitor currently in Phase I evaluation in patients with advanced cancers.

Development of Hsp90 Inhibitors as Novel Therapeutics for Alzheimer's Disease

Gabriela Chiosis
Memorial Sloan-Kettering Cancer Center

Both malignant transformation and neurodegeneration, as it occurs in Alzheimer's disease, are complex and lengthy multistep processes characterized by abnormal expression, post-translational modification, and processing of certain proteins. To maintain and allow the accumulation of these dysregulated processes, and to facilitate the step-wise evolution of the disease phenotype, cells must co-opt a compensatory regulatory mechanism. In cancer, this role has been attributed to heat shock protein 90 (Hsp90), a molecular chaperone that maintains the functional conformation of multiple proteins involved in cell-specific oncogenic processes. In this sense, at the phenotypic level, Hsp90 appears to serve as a biochemical buffer for the numerous cancer-specific lesions that are characteristic of diverse tumors. We propose a similar role for Hsp90 in neurodegeneration, and present data suggesting that Hsp90 can act as a regulator of pathogenic changes leading to the neurodegenerative phenotype in Alzheimer's disease. We also present our efforts towards the development of Hsp90 inhibitors as possible therapeutic interventions in Alzheimer's disease.



Claudio Cuello, MD, Dsc, FRSC, McGill University

Dr. A. Claudio Cuello is currently the McGill Charles E. Frosst/Merck Chair in Pharmacology, a Visiting Professor at Oxford University and Adjunct Professor of Neuropharmacology at the Scripps Research Institute (La Jolla, Ca). He is a past Staff Scientist for the Medical Research Council in Cambridge, U.K. (1975-1978), Lecturer (Associate Professor) in Neuropharmacology and Neuroanatomy at Oxford University and Fellow and Medical Tutor at Lincoln College, Oxford (1978-1985). Dr. Cuello leads a research team working on multidisciplinary aspects of aging and cellular animal models of Alzheimer's disease neuropathology. He has made pioneering publications on dendritic release of neurotransmitters, the localization

and role of central and peripheral neuropeptides, trophic factor-induced repair and synaptogenesis and novel applications of monoclonal antibodies in the neurosciences. His research activities have been conducted at the University of Buenos Aires in Argentina, the University of California in San Francisco (USA), the Universities of Cambridge and Oxford (England), and McGill University in Canada. He has received numerous recognitions in Canada, such as the Heinz Lehman Award, the Novartis Award and has been named a Fellow of the Royal Society of Canada. He is an Honorary Professor at the Norman Bethune University (China) and at the University of Buenos Aires (Argentina), as well as Doctor Honoris Causa at the Federal University of Ceara (Brazil) and Honorary Doctor in Medicine at Kuopio University (Finland). Recently, he was named Highly Cited Neuroscientist by the ISI (Institute of Scientific Information, USA). His scientific accomplishments until 2001 have been summarized in *"The History of Neuroscience in Autobiography"* (Sponsored by the Society for Neuroscience, USA), ed. Larry R. Squire, Academic Press, NY, 2001.

Combined Experimental Therapy in an Alzheimer's Transgenic Model - A Progress Report

A. Claudio Cuello, M. T. Ferretti, M. Bruno, W. Leon, V. Partridge, S. Allard, A. Ducatenzeiler.
Department of Pharmacology and Therapeutics, McGill University, Montreal, Quebec H3G 1Y6 Canada

We have shown in cell and transgenic animal models that the pathological accumulation of intracellular A β peptides (as also observed in Alzheimer's disease and Down's Syndrome) leads to an alteration in cell organelles and proteomic patterns, as well as a dysregulation of the Erk signaling pathway and behavioral impairments. Recently, we have gathered evidence that indicates that this pathological intracellular A β material is oligomeric in nature, and that cortical neurons burdened with intracellular A β recruit activated microglia and trigger an inflammatory process, preceding the extracellular A β pathology; i.e. a "pre-amyloid plaque" inflammatory process. We have also demonstrated that the injections of A β oligomers in the hippocampus of naïve rats produce a similar inflammatory response, which is blocked by the administration of minocycline. Minocycline administration in a transgenic animal model at these early stages of the AD-like amyloid pathology prevented the inflammatory responses and improved the learning and memory performances. In light of the fact that some agents, such as scylloinositol (McLaurin *et al.* 2006. *Nat Med* 12:801-8), have been reported to neutralize A β oligomers and to improve behavioral parameters in AD-like transgenic models, we are investigating the effects of these agents (minocycline and scylloinositol) alone, or in combination, on the intracellular A β load, inflammatory markers and animal behavior. In this presentation we will discuss the results so far obtained for this ongoing investigation.

Acknowledgements: This research has been supported by funds from the CIHR (grant #MOP-67170) and ISOA (grant #271224).



Douglas Feinstein, PhD, University of Illinois at Chicago

Dr Doug Feinstein obtained his PhD in cell biology from Johns Hopkins University, acquired post-doctoral training in the Department of Neuropharmacology at the Research Institute of Scripps Clinic, and took his first faculty position in the Department of Neurology at the Cornell University Medical College. He is currently Research Professor in the Department of Anesthesiology at the University of Illinois in Chicago. His major research focus is to understand and regulate inflammatory responses in neurodegenerative diseases including AD and MS. He is an active member of the American Society for Neurochemistry, and is currently president-elect.

Anti-amyloidogenic Effects of Noradrenaline and PPARdelta Agonists

Douglas Feinstein
University of Illinois at Chicago

Inflammatory responses in brain contribute to pathogenesis in a variety of neurological conditions including AD. We have been characterizing the ability of various anti-inflammatory treatments to reduce damage in transgenic mouse models of AD (TgAPP mice). We have focused attention on the endogenous neurotransmitter noradrenaline (NA), since loss of noradrenergic neurons in the Locus coeruleus (LC) occurs during AD, and we have shown that experimental lesion of LC exacerbates inflammation as well as amyloid burden. We are also evaluating agonists of peroxisome proliferator activated receptors, since several reports describe anti-inflammatory and neuroprotective properties of these drugs, as well as rapid decreases in amyloid burden. In the current work, we tested these two interventions using 5xFAD TgAPP mice which harbor 2 mutations in Presenilin 1 and 3 in Amyloid Precursor Protein, and develop plaques by age 6-8 weeks. Treatment with an alpha-2 adrenergic receptor antagonist to raise NA levels showed a trend toward decreasing plaque burden. In contrast, treatment with a selective PPAR δ agonist (provided in the chow for 1 month) significantly decreased plaque burden, neuronal damage, and inflammation in both male and female mice. These changes were associated with an increase in expression of neprilysin and insulin degrading enzyme, which could contribute to increased amyloid clearance. Further studies using PPAR δ agonists therefore appear warranted.



S. Prasad Gabbita, PhD, P2D Biosciences

Dr. Gabbita received his PhD in Toxicology from the University of Kentucky, Lexington in 1996. Dr. Gabbita examined the role of mitochondrial respiration in lipid and protein oxidation as part of his PhD thesis. Dr. Gabbita pursued postdoctoral studies at the Sanders Brown Center on Aging, Lexington where he evaluated the extent of free-radical mediated of nuclear and mitochondrial DNA oxidation and loss in protein and enzyme function in AD. Dr. Gabbita continued his post-doctoral training at the Oklahoma Medical Research Foundation, Oklahoma City, where he examined novel antioxidants and anti-neuroinflammatory compounds as potential CNS therapeutics. Dr. Gabbita joined P2D in 2000 and now heads its Research and Development activities. Dr. Gabbita's research is focused on developing novel therapeutic agents to treat neurodegenerative diseases such as AD, PD, TBI and ALS. Dr. Gabbita is also developing protein biomarker-based, point-of-care diagnostics for rapidly detecting traumatic brain injury and spinal cord injury in a neuroemergency setting.

Small Molecule TNF-Alpha Inhibitors for Alzheimer's Disease

S. Prasad Gabbita, PhD
P2D Biosciences

P2D Biosciences is evaluating small molecule TNF-alpha inhibitors as "first-in-class" AD drug treatments. Multiple lines of preclinical and clinical evidence suggest that the neuroinflammatory cytokine TNF-alpha is a "drugable" target that upon modulation modifies the course of AD progression and blocks cognitive decline. P2D's small molecule TNF-alpha inhibitors are analogs of thalidomide. Studies suggest that thalidomide destabilizes TNF-alpha mRNA thus decreasing TNF-alpha protein levels. Preclinical studies suggest that thalidomide may be effective in treating AD by targeting TNF-alpha. A recent study demonstrated that thalidomide blocked TNF-alpha elevation and protein nitration in the hippocampus and importantly improved recognition memory in an AD mouse model. In a separate study, thalidomide was found to be an effective inhibitor of gliosis, vascular changes and TNF-alpha leading to neuroprotection in AD mice. P2D's preliminary studies demonstrate that our lead TNF-alpha inhibitors exhibit up to 66-fold stronger TNF-alpha inhibition in vitro than their parent, thalidomide. Peripheral administration of our TNF-alpha inhibitors blocked brain TNF-alpha elevation in a rat lipopolysaccharide (LPS) neuroinflammation model. With ADDF's biotechnology grant award, we will determine the effect of our lead compounds on brain TNF-alpha levels, synaptic integrity, glial and iNOS activation and learning and memory employing a triple-transgenic AD mouse model.



Illana Gozes, PhD, Tel Aviv University and Allon Therapeutics, Inc.

Dr. Gozes is a founder and Chief Scientific Officer of Allon Therapeutics Inc (Vancouver, Canada) and Professor of Clinical Biochemistry, the Lily and Avraham Gildor Chair for the Investigation of Growth factors at Tel Aviv University (TAU), where she directs the Adams Super Center for Brain Studies, the Edersheim Levie-Gitter Institute for Functional Brain Imaging. At the Sackler Faculty of Medicine, Professor Gozes heads the Dr. Diana and Zelman Elton (Elbaum) Laboratory for Molecular Neuroendocrinology. Professor Gozes serves or has served as a member (or chair) of several faculty/university/national and international committees and is currently the Editor-in Chief of the Journal of Molecular Neuroscience. Professor Gozes was recently elected as President elect of the Israel Society for Neuroscience. Professor Gozes has received a number of scientific awards and prizes for her work, including the Landau Prize for excellent PhD dissertation, the Juludan Prize and later the Teva Prize for opening new horizons in medical research in Israel, the Bergmann prize and later the Neufeld award for leading grant proposals from the US-Israel Binational Science Foundation. Prof. Gozes was recently selected as the 2007 recipient of the Tel Aviv University Applied Research Award. She is co-inventor of more than 25 patents and patent applications, including the composition of matter patent on AL-108, Allon's lead compound formulation. Professor Gozes received a Ph.D. from The Weizmann Institute of Science, and a postdoctoral fellow from Massachusetts Institute of Technology. She was a research associate and visiting scientist at the Salk Institute and the Scripps Clinic and Research Foundation and a Fogarty-Scholar-in-Residence at the National Institutes of Health (USA).

Updates on AL-108: Case Study for Drug Discovery and Development toward Cognitive Enhancement and Neuroprotection

Illana Gozes^{1,2}

¹*Adams Super Center for Brain Studies, Gildor Chair, Sackler Faculty of Medicine Tel Aviv University, Israel;* ²*Allon Therapeutics Inc. Vancouver, Canada*

AL-108 is the intranasal formulation of a neuroprotective peptide (termed NAP), currently in clinical development for Alzheimer's disease and cognitive-impairment in schizophrenia. The discovery of NAP (single letter code: NAPVSIPO) was made possible by peptide activity scanning of activity-dependent neuroprotective protein (ADNP), a protein essential for brain formation and function. NAP is a peptide snippet of ADNP with bioavailability and clean toxicological profile. NAP is associated with microtubule stability and reduction in tau (tubulin-associated unit) pathology. Microtubules are key elements in the cellular cytoskeleton. As dynamic structures, microtubules are also involved in axonal transport and the formation and maintenance of synaptic plasticity. Tau binds to the microtubule subunit - tubulin and enhances microtubule formation. Dysfunctional brain microtubules are associated with neuronal death and often time with the accumulation of pathological forms of tau, as in the case of Alzheimer's disease and other tauopathies. In schizophrenia, a link has been suggested to the STOP proteins (stable tubule-only polypeptide). A case study from the NAP discovery and AL-108 development program will be presented to illustrate how discovery research and preclinical data was used toward Phase 2 clinical trials, targeting prevalent intractable CNS diseases. Partial reduction in ADNP resulted in cognitive impairments and tau pathology, which were ameliorated in part by intranasal NAP treatment. Similar results were obtained in Alzheimer's related animal models. Allon Therapeutics Inc. (www.allontherapeutics.com) recently released top-line results of a Phase IIa clinical trial showing that its drug AL-108 has a positive impact on memory function in patients with amnesic mild cognitive impairment (aMCI), a precursor to Alzheimer's disease (AD).



Varghese John, PhD, Buck Institute

Varghese John is currently Director of the Alzheimer's Drug Discovery Network at the Buck Institute for Age Research. The Drug Discovery Network is developing novel therapeutic approaches to Alzheimer's disease in collaboration with Dr. Dale Bredesen, Professor and Founding President of the Buck Institute for Age Research. Previously, Varghese was at Elan Pharmaceuticals for 18 years and led a team of medicinal chemists developing drugs for CNS diseases with a focus on AD. His work at Elan included development of potent inhibitors for BACE and γ -secretase, key enzymes in formation Abeta and amyloid plaques. He has several scientific publications and patents in his field. He is also Founding Scientist of a startup company E-SOC, Inc. focused on Parkinson's disease.

Screening for Alzheimer's Therapeutics Based on a Novel Target

Varghese John, Matthew Hart, Veronique Corset, Veronica Galavan, Clare Peters-Libeu, Dale E. Bredesen
Buck Institute

In Alzheimer's disease (AD), brain cells and brain cell connections are lost, leaving the brain unable to function normally. The reason for the neuronal cell loss is not yet understood, but a great deal of attention has been focused on the aberrant cleavage pathway of the amyloid precursor protein (APP) leading to the production of $A\beta$ peptide which collects in the brains of patients with Alzheimer's disease. Three protease cleavages are known to occur in the aberrant processing of APP. These include the β -secretase and γ -secretase cleavages that result in the production of neurotoxic $A\beta$ peptide along with a third C-terminal protease cleavage that occurs in the intracellular region of APP. This C-terminal cleavage of APP gives rise to a second neuronal cell-killing molecule called C31 (derived from the 31 amino acids from the carboxyterminal tail of APP), which was discovered by our laboratory at the Buck Institute.

We have found that the C-terminal cleavage is enhanced in patients with Alzheimer's disease. We also showed that if we genetically blocked this C-terminal cleavage of APP, the degree of cell death was reduced dramatically. Furthermore, using a transgenic mouse that modeled Alzheimer's disease, we found that we can prevent the C-terminal proteolysis *in vivo* by mutating APP695 (Asp664→Ala), and this point mutation in APP results in Tg mice lacking the AD phenotype. Therefore, identifying molecules that mimic the genetic blockage may be a useful strategy for developing novel AD therapeutics.

We are grateful to the ISOA for its grant support on this project. This has enabled us to begin setting up an HTS assay system for screening small molecule compound libraries to identify novel molecules that would inhibit the aberrant processing of APP resulting in the production of $A\beta$ and the C-31 peptide. The setup of the HTS assay system for screening will be described along with early screening data. In addition we are also developing an HTS assay system to identify molecules that would enhance the normal α -secretase pathway and our strategy in this regard will also be described in this presentation.



Anthony J. Koleske, PhD, Yale University

Dr. Anthony J. Koleske is an expert in understanding the biochemical mechanisms that control changes in cell shape and movement. After receiving a B.S. in Biochemistry and Molecular Biology at the University of Wisconsin-Madison, Dr. Koleske performed his Ph.D. studies with Dr. Richard Young at the Whitehead Institute/Massachusetts Institute of Technology. For his Ph.D. thesis, Dr. Koleske discovered the RNA polymerase II holoenzyme, an important advancement in understanding how gene transcription is turned on. Dr. Koleske went on to do a postdoctoral fellowship with Nobel Laureate Dr. David Baltimore at the Rockefeller University and later at M.I.T., where he began his work studying cellular functions of Abl family kinases, essential regulators of the cytoskeleton. Dr. Koleske joined the Department of Molecular

Biophysics and Biochemistry at Yale University in 1998, where he is currently a tenured Associate Professor and has a joint appointment in the Department of Neurobiology. Dr. Koleske is the recipient of numerous awards including a Jane Coffin Childs Postdoctoral Fellowship, a Special Fellowship from the Leukemia and Lymphoma Society, a NARSAD Young Investigator Award, and an Established Investigator Award from the American Heart Association. He has served on several N.I.H. Study Sections and is currently co-Chair of the Basic Science Study Section for the American Heart Association.

Does Inhibition of Rho Signaling Protect Against Synapse Loss and Dendritic Regression in Alzheimer's Disease Mouse Models?

Brian A. Couch and Anthony J. Koleske

Department of Molecular Biophysics and Biochemistry, Yale University, New Haven, CT, 06520

The brains of individuals with Alzheimer's Disease (AD) exhibit significant regression of hippocampal and cortical dendritic arbors accompanied by a loss of synapses. Importantly, synapse loss, and not neuron death, correlates with the degree of dementia in AD patients. Therefore, preventing dendritic regression and synapse loss represents a major therapeutic target for AD treatment. The long-term goals of this project are to determine the molecular mechanisms that underlie dendritic regression and synapse loss in AD and to block this regression using small molecule inhibitors.

Rho GTPase regulates changes in axon and dendrite structure by stimulating Rho kinase (ROCK) to phosphorylate myosin regulatory light chain, leading to increased actomyosin contractility. Hyperactive Rho signaling in mature neurons leads to dendritic spine and synapse loss and dendritic regression. To test the hypothesis that inappropriate Rho signaling contributes to dendritic regression and synapse loss in AD, we have administered the ROCK inhibitor fasudil to AD model mice via intracerebroventricular infusion. Evaluation of synapses, dendrite arbors, and recognition memory will reveal the extent to which fasudil treatment protects against neurodegeneration in these mice. Results from these experiments will be presented during the meeting.

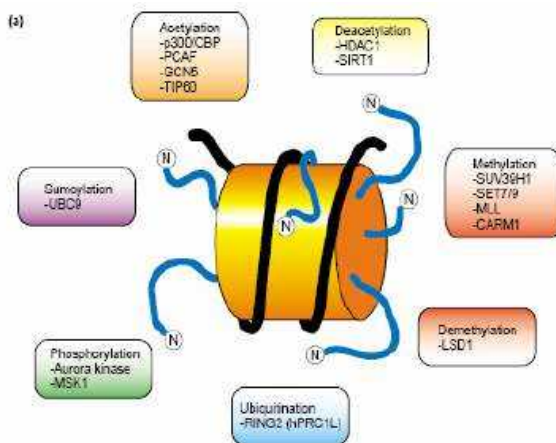


Alan P. Kozikowski, PhD, University of Illinois at Chicago

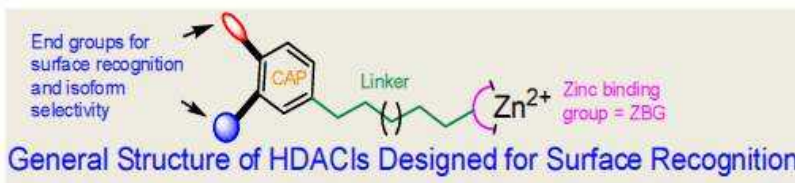
Dr. Alan P. Kozikowski is a Professor of Department of Medicinal Chemistry and Pharmacognosy at the University of Illinois at Chicago and Director of International Drug Discovery Institute. He has published more than 400 peer reviewed research papers in a variety of prestigious scientific journals and also has over 100 patents. He has an AD drug in phase II clinical trials, an Akt inhibitor going into Phase 0 trials at the NCI last year, and a prostate cancer imaging agent now in phase I clinical trial.

Chromatin Remodelers for Recovery of Learning and Memory

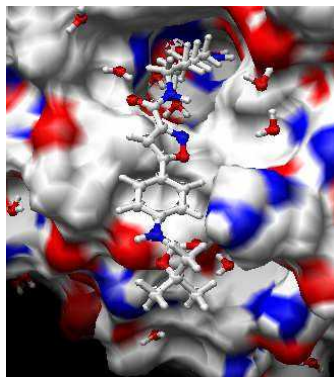
HDAC inhibitors (HDACIs) are able to reactivate silenced genes, and these compounds have been shown to be of some value in the treatment of cancer [CTCL], and possibly even neurological disorders as well as certain parasitic diseases such as malaria. In our efforts to identify HDACIs that



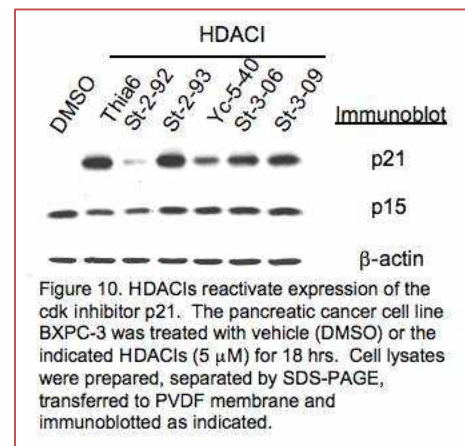
From DDT - Volume 11, Number 3/4 - February 2006



may show an improved therapeutic profile, we have sought to identify compounds that may show enhanced levels of HDAC isozyme selectivity, as it is believed that some of the undesirable side effects of these agents may relate to their overall lack of enzyme selectivity. We have thus been investigating the design, synthesis, and testing of compounds containing various CAP residues that may interact differentially with the surface areas of these enzymes outside their catalytic gorge regions, as well as to more broadly assess the effect of variations in the zinc binding groups. In this presentation I shall summarize our current efforts in this exciting field of epigenetics, and present the results of both cell and animal studies. In particular I will present data demonstrating the superiority of thiol-based HDACIs in models of oxidative stress and in the fluid percussion model of traumatic brain injury.



Compound **8** docked in the binding site of the current homology model of HDAC6. The HDAC6 homology model was built based on the X-ray crystal structure of hDAC7 (2PQP) as a template. The ZBG hydroxamic acid and the six methylene group bind deep inside the narrow binding pocket. The bound ligand appears to interact with only one region of the HDAC surface with the *t*-butyl group buried in a hydrophobic cleft.





Jeff Kuret, PhD, Ohio State University

Dr. Kuret is a Professor of Molecular and Cellular Biochemistry at The Ohio State University. He completed his BS degree in biochemistry at the University of California, Los Angeles, and conducted graduate work with Professor Howard Schulman at Stanford University. After earning his PhD degree in Pharmacology, he joined the laboratory of Sir Philip Cohen in the Medical Sciences Institute, Dundee, Scotland as a postdoctoral fellow, and served on the faculties of Cold Spring Harbor Laboratory and Northwestern University. He currently serves on the *Synapse Cytoskeleton and Trafficking (SYN)* and *Drug Discovery (MNPS-C)* review panels at the NIH Center for Scientific Review.

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

Tau Aggregate Inhibitors: A Medicinal Chemistry Point of View

Jeff Kuret, Ph.D.

Center for Molecular Neurobiology, The Ohio State University College of Medicine, Columbus, OH 43210

The interaction of small molecules with tau monomers and filaments was assessed using *in vitro* and cellular aggregation assays. The experiments revealed that small molecules interacted with recombinant full-length tau monomers and fibrillar tau aggregates in three distinct modes. First, in the high concentration regime (>10 micromolar), molecules such as Congo red efficiently promoted tau filament formation through a nucleation-elongation mechanism involving a dimeric nucleus and monomer-mediated elongation. Use of agonists to characterize the aggregation propensity of naturally-occurring isoforms and of missense mutations identified the rate limiting steps in the pathway that were sensitive to changes in tau primary structure. Second, in the low concentration regime (<1 micromolar), other ligands, including cyanine dyes, displayed aggregation antagonist activity. A structure activity relationship for thiocarbocyanines showed that antagonist potency *in vitro* could be maintained while calculated physical properties were optimized for proof of concept studies in biological models. Finally, certain compounds bound mature tau fibrils with varying affinities at multiple binding sites. For some ligands, >10-fold selectivity for tau aggregates relative to filaments composed of beta-amyloid or alpha-synuclein could be demonstrated at the level of binding affinity. Together these observations suggest that small-molecules have utility for interrogating the tau aggregation pathway, for inhibiting neuritic lesion formation, and potentially for development of selective pre-mortem contrast agents for whole brain imaging of neurofibrillary lesions.



Thomas Lanz, Pfizer, Inc.

Thomas Lanz is a Senior Scientist in Neurosciences Biology R&D at Pfizer in Groton, CT. Tom has spent the past seven years trying to understand the biology underlying Alzheimer's disease pathogenesis and disease progression, and has worked on a number of AD targets. Particular focus has been given to gamma secretase, and he has authored several publications dealing with the pharmacodynamics of gamma secretase inhibitors. Other notable areas of interest have included AD biomarkers, Abeta passive immunotherapy, and synaptic deficits in AD models. Prior to his work in Alzheimer's disease, Tom studied physiology and behavior

at the University of CT and Colgate University, and functional neuroanatomy at Vanderbilt University and the National Institute of Mental Health.

Phosphodiesterases and Synaptic Plasticity: Novel Approaches to the Treatment of Alzheimer's Disease

Thomas Lanz

Pfizer Global Research & Development, Groton, CT

Alzheimer's disease (AD) is characterized by synaptic dysfunction and cognitive deficits antecedent to significant plaque and tangle pathology. Cognitive decline correlates with an overt loss of synapses and dendritic spines as assessed in post-mortem AD brains. Soluble forms of A β are thought to contribute to these early deficits as evidenced by various in vitro and in vivo models, and A β production has itself been linked to synaptic activity. Thus stabilizing synapses may be a useful strategy for preserving cognitive function and potentially slowing disease progression in AD. The phosphodiesterase (PDE) family of genes is responsible for metabolically inactivating the second messengers cAMP and cGMP, providing spatial and temporal control of cyclic nucleotide signaling cascades. cGMP signaling has been shown to be integral to normal synaptic function and plasticity, and deficits in this signaling pathway have been demonstrated in AD brain and in mouse models. PDE9 is the highest affinity cGMP PDE, and exhibits expression in key areas of the brain relevant to AD. Inhibition of PDE9 activity by genetic or pharmacologic manipulation elevates cGMP levels in the brain. The consequences of this elevation include enhancement of hippocampal long-term potentiation, improved memory consolidation, enhanced neurite outgrowth, increased density of mature dendritic spines in the hippocampus, and impacts on gene expression in AD-relevant signaling pathways. Thus PDE9 inhibitors are being proposed as synaptic stabilizing agents to preserve cognitive function in AD patients.



Daniel Laskowitz, MD, Duke University

Dr. Laskowitz is a graduate of Duke University School of Medicine (1991) and Brown University (1987), where he majored in Neuroscience. After completing his Neurology Residency at the University of Pennsylvania in 1995, he returned to Duke to complete fellowship training in Neurocritical Care and Stroke. He has remained active in both laboratory-based and clinical research, and completed his Masters of Health Science in Clinical Research in 2003. He currently serves as the Fellowship Director in Neurocritical Care and Director of the Neurovascular Laboratory. Dr. Laskowitz attends on the Neurosciences Intensive Care Unit, a multidisciplinary unit in which patients with life-threatening neurological diseases such as stroke, trauma, and intracranial hemorrhage are cared for. He also heads a laboratory that uses molecular biology, cell culture, and animal modeling techniques to examine the CNS response to acute injury. These results are translated to clinically relevant small animal models with the ultimate goal of exploring new therapeutic interventions in the clinical setting of stroke, intracranial hemorrhage, and closed head injury. The results of this work have been translated to several pilot clinical studies examining new treatment approaches for patients in the Neurocritical Care Unit, such as the use of statins to improve outcomes after subarachnoid hemorrhage, and the development of a novel point-of-care diagnostic test to rapidly identify and expedite the care of patients with acute stroke. Dr. Laskowitz's laboratory has also focused on genetic influences that modify how the brain responds to injury. In particular, he has focused on the role that variants of the apolipoprotein E play in recovery from different forms of acute brain injury.

ApoE Therapeutics

Daniel T. Laskowitz^{1,2}, Pingping Song¹, Haichen Wang¹, Brian Mace³, Patrick M. Sullivan³, Michael P Vitek^{1,2,4}, Hana N. Dawson¹

Departments of ¹ Medicine (Neurology), ² Neurobiology, ³ Medicine (Geriatrics), Duke University Medical Center, Durham, NC 27710; ⁴Cognosci, Inc, Research Triangle Park, NC 27709

The neuropathology of Alzheimer's disease (AD) is associated with progressive cognitive impairment. Despite development of symptomatic therapies, there remains no proven disease modifying intervention. APOE polymorphism has been identified as an important risk factor for the development of late onset familial and sporadic AD (1). In the current study, we examine the role of traumatic brain injury (TBI) in accelerating AD pathology in double transgenic animals expressing the common human APOE alleles and mutated amyloid precursor protein (APP^{V717F}). In these animals, the characteristic features of AD pathology, such as A β deposition, microgliosis, neuronal degeneration, synaptic loss, and tau phosphorylation, were present at 6 months of age after exposure to TBI. The presence of APOE4 allele was associated with increased A β deposition, microgliosis, and tau phosphorylation. The administration of an apoE-mimetic peptide markedly reduced the development of AD pathology in mice homozygous for APOE3, with minimal effects observed in the APOE4 homozygotes. Similarly APOE3/APOE4 heterozygous mice also benefited from the peptide treatment. These results demonstrate that TBI accelerates the cardinal neuropathological features of AD in PDAPP^{V717F} animals and furthermore establishes the potential for apoE mimetic therapies in reducing neuropathology associated with Alzheimer's disease.



Frank Longo, MD, PhD, Stanford University

Dr. Longo received his MD in 1981 and PhD in Neurosciences in 1983 from the University of California, San Diego. Following an internship in medicine at NYU/VIA, he trained as a resident in neurology and fellow in neurobiology at University of California, San Francisco. While at UCSF he created the Neurogenetics Clinic which was the first West Coast site in the U.S. to offer DNA testing for families with Huntington's disease. He also led the creation of a national referral center for deep brain stimulation for Parkinson's disease and contributed to the development of programs in dementia, epilepsy and other areas. At UCSF he became professor and vice chair of the Department of Neurology and in 2001 he was recruited to become chair of the Department of Neurology at the University of North Carolina, Chapel Hill. While at UNC, Dr. Longo launched or expanded programs for Alzheimer's disease and other dementias, stroke, epilepsy, sleep disorders, multiple sclerosis and Parkinson's disease. In January 2006, Dr. Longo became chair of the Department of Neurology and Neurological Sciences at Stanford where he is focused on building and expanding multidisciplinary programs in neurology and neuroscience. In 2006 he was named a Stanford Fellow. Dr. Longo's research team focuses on elucidating novel mechanisms that prevent neural degeneration and promote regeneration. He and his colleagues have pioneered the development of small, drug-like, molecules that target neurotrophin receptors to delay onset of or slow progression of Alzheimer's and other neurodegenerative disorders.

Development of p75 Neurotrophin Receptor Small Molecule Ligands for Alzheimer's Therapy

Frank M. Longo, MD, PhD^{1,2,3} and Stephen M. Massa, MD, PhD⁴

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The p75 neurotrophin receptor (p75^{NTR}) is expressed by neurons preferentially affected in Alzheimer's disease (AD). We have developed several generations of first-in-class small molecule, non-peptide p75^{NTR} ligands that activate survival signaling to inhibit neuronal death. *In vitro* studies have demonstrated that small molecule p75^{NTR} ligands inhibit A β -induced neuritic dystrophy, death of dissociated neurons and death of pyramidal neurons in hippocampal slice cultures. Signaling studies reveal that ligands inhibit A β -induced activation of multiple deleterious signaling pathways potentially contributing to AD pathology and synaptic dysfunction. Compounds also block A β -induced tau phosphorylation and prevent A β -induced inactivation of AKT and CREB. In hippocampal slice/LTP studies performed in collaboration with Dr. Ottavio Arancio at Columbia University, compounds block LTP impairment caused by exogenous A β , and restore LTP in hippocampal slices derived from mutant PS1/APP transgenic mice. *In vivo* studies demonstrate favorable drug development profiles; the ability to reverse basal forebrain cholinergic neuron atrophy in wild-type aged mice; and the capacity to significantly reduce neuritic dystrophy in a well characterized model of mutant APP transgenic mice. IND enabling studies are underway.

Studies have been funded by the Institute for the Study on Aging (ISOA), the Alzheimer's Drug Discovery foundation (ADDF), the Alzheimer's Association, the Eastern Chapter of the North Carolina Alzheimer's Association and a translational U01 from the National Institute on Aging (NIA).



Eva-Maria Mandelkow, PhD, Max Planck Unit for Structural Biology

Eva-Maria Mandelkow received her MD degree at the University of Hamburg, German, and worked for several years as an intern at university hospitals in Hamburg and Heidelberg. She then switched to basic biomedical research, obtained her PhD at the Max-Planck-Institute for Medical Research in Heidelberg, and worked as a postdoctoral fellow at Brandeis University (USA) and in Heidelberg. Her scientific interests center around the biochemistry, structure and cell biology of the cytoskeleton, notably microtubules, motor proteins, and microtubule-associated proteins. Among these proteins, Tau protein is unique because it forms pathological aggregates in Alzheimer's disease and several other neurodegenerative diseases. The focus of her present research is the elucidation of the physiological and pathological functions of Tau protein in cell and animal models of neurodegeneration, and the identification of targets for intervention. Eva-Maria Mandelkow is currently a principal investigator at the Max-Planck-Unit for Structural Molecular Biology in Hamburg, Germany.

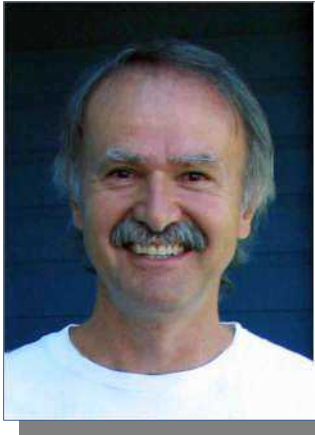
MARK as a Target for Neurodegenerative Disease

Eva-Maria Mandelkow, PhD

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Aggregated forms of tau protein is a hallmark of several tauopathies, including Alzheimer disease, FTDP-17, and others. In these tau aggregates, tau is also in a state of elevated phosphorylation which precedes aggregation, leading to a widely-held assumption that the phosphorylation of tau primes it for aggregation. However, a detailed analysis of phosphorylation sites, kinases, and tau domains suggests that the origins and pathways of tau's toxicity to neurons are heterogeneous. Some kinases (e.g. those of the MARK family, or, more broadly of the AMPK/SNF1 family) phosphorylate tau at the KXGS motifs of the repeat domain and thereby cause the detachment from microtubules, the major binding partner of tau in neurons. The detachment is a prerequisite for subsequent aggregation, and therefore the inhibition of MARK kinases represents a possible approach to reduce tau aggregation and to stabilize microtubules (Schneider & Mandelkow, Neurother. 2008).

These pathways are modulated by two features: On one hand, the phosphorylation of tau at the KXGS motifs tends to inhibit tau aggregation (Schneider et al., Biochem 1999), but it also tends to suppress the interaction with the CHIP-Hsp90 complex, thereby reducing the degradation by the proteasomal system and leading to further accumulation in the cytosol (Dickey et al., PNAS 2008). MARK can be inhibited by small molecules occupying the kinase catalytic site, but in addition it can be up- or downregulated by other components of the multisubunit complex to which MARK is anchored. One example is the binding of kinase PAK5 which regulates the dynamics of actin microfilaments but stabilizes microtubules via inhibiting MARK (Matenia et al., MBC 2005). A second example is the binding of the kinase TESK1 and the adaptor protein Spred1 which inhibits the kinase MARKK and thereby prevents the activation of MARK (Johne et al., MBC 2008). Thirdly, MARK can be activated by phosphorylating T208 in the regulatory loop by MARKK or LKB1, but inhibited by phosphorylating S212 by GSK3b (Timm et al., JBC 2008). Thus, the inhibition of GSK3b (a popular target for reducing the proline-directed phosphorylation of tau) leads to the activation of MARK and phosphorylation of the repeat domain. One consequence is that in the PI3Kinase pathway, the kinase Akt/PKB inhibits GSK3b by phosphorylating S9, thereby leading to the activation of MARK. The examples illustrate the highly interconnected regulatory pathways that affect tau aggregation and microtubule stability.



Karoly Nikolich, PhD, Stanford University and Amnestix, Inc.

Karoly Nikolich has been CEO of Amnestix, Inc. since its founding in 2007. He has also served as the US partner and advisor of dievini Hopp investments since 2007, supporting the portfolio companies in strategic activities. He has also been board and SAB member of several biotech companies. Before joining Amnestix and dievini, he was executive director of the Neuroscience Institute at Stanford University. Karoly co-founded several biotech companies, including AGY Therapeutics with Bob Swanson in 1998. He started his career in the biotech industry as a scientist at Genentech 25 years ago where he initiated and built the company's first neuroscience research program. Later, he was Vice President of Research at Lynx Therapeutics (acquired by

Solexa/Illumina). Karoly is also Consulting Professor at Stanford University Medical School and was formerly Adjunct Professor at the University of Southern California. As a scientist he co-authored 125 publications.

Karoly is a graduate of Eotvos University in Budapest, Hungary, and conducted postdoctoral studies at Tulane University in New Orleans and at the University of California San Francisco.

KIBRA as a Novel Target for Alzheimer's Disease

Karoly Nikolich, Matt Huentelman, Dietrich Stephan
Amnestix, Inc., Burlingame, California, and Translational Genomics Research Institute, Phoenix, Arizona

KIBRA is a multidomain protein expressed in hippocampal and cortical neurons. KIBRA was identified in a genome wide association study of several independent, cognitively normal cohorts to be associated with memory performance. Functional magnetic resonance imaging detected differential hippocampal activation patterns during memory retrieval in individuals with different KIBRA alleles. These data suggested a role for KIBRA in human memory.

KIBRA is a multi-phosphorylated protein that interacts with neuronal proteins involved in plasticity. The RhoA/ROCK pathway and the ceramide pathway have been identified to regulate KIBRA activity. Peripheral administration of the ROCK inhibitor fasudil and hydroxyfasudil improved hippocampal-based spatial learning and working memory and influences the expression of memory-related genes in aged rats. The retinoid, fenretinide, also improved spatial learning and working memory in aged rats. Conversely, inhibition of PKCzeta reduced cognitive performance in young rats. These findings support the role of ROCK inhibitors and retinoids acting on KIBRA activity on learning and memory, and suggests their potential for the treatment of learning and memory deficits in humans. We are also evaluating direct KIBRA phosphorylation and activation based assays for screening for novel agents.



Juan Sanchez-Ramos, MD, PhD, University of South Florida

Dr. Juan Sanchez-Ramos is Professor of Neurology at the University of South Florida (USF) in Tampa where he holds the Helen Ellis Endowed Chair for Parkinson's Disease Research. He is an Investigator with the NIA-sponsored ADRC at the Johnnie Byrd Alzheimer's Disease Research Center & Institute. He is also the Director of the HDSA Center of Excellence at USF, a comprehensive clinic dedicated to patients with Huntington's disease.

In addition to teaching medical students and neurology residents, he directs a basic research laboratory with active projects in neurodegeneration and adult stem cell biology.

G-CSF Reduces Brain Amyloid, Increases Expression of Synaptophysin and Improves Cognition in a Mouse Model of Alzheimer's Disease

J. Sanchez-Ramos, PhD, MD

University of South Florida & Byrd Alzheimer's Disease Research Institute, Tampa, FL

Filgastrim (G-CSF) is a multi-modal hematopoietic growth factor which also has profound effects on the diseased central nervous system. Administration of G-CSF to cognitively-impaired Alzheimer's Disease (AD) transgenic mice (APP+PS1) resulted in a) significantly improved cognitive performance, b) decreased β -amyloid deposition in hippocampus and entorhinal cortex, c) reduced pro-inflammatory cytokine levels in blood and d) augmented microglial activity around and within amyloid deposits mediated, in part, by enhanced recruitment of bone-marrow derived microglia. Improved cognition in AD mice was associated with increased areas of synaptophysin immunoreactivity in hippocampal CA1 and CA3 regions. These results support strategies to reduce brain A β and reverse synaptic dysfunction to improve cognitive performance. Given that G-CSF is already utilized clinically to stimulate hematopoietic stem cell production, these research findings will be readily translated into clinical trials to reverse or forestall the progression of dementia in AD.



Horacio Uri Saragovi, PhD, McGill University

Dr. H. Uri Saragovi is a Professor in the Departments of Pharmacology & Therapeutics, and Oncology at McGill University in Montreal. He has held key positions in a variety of Groups and Institutes including: the McGill Center for Translational Research, the McGill Chemical Biology Program, the Jewish General Hospital-Lady Davis Research Institute, the Bloomfield Center for Neuroscience, the inter-University Group for Research in Medicines (GRUM), and others. Professor Saragovi has authored more than 80 scientific papers in highly respected peer-review journals and has 11 patents for the development of peptidomimetics, rational antibody design, drug-conjugate linkers, and therapeutic targets. He is a member of editorial review boards of leading scientific journals, and sits or has served on grant review panels at the NIH (USA),

the CIHR (Canada) and the NCI (USA and Canada).

Validation of Trk (and p75) Receptors as Therapeutic Targets in Neurodegenerative Disorders

H. Uri Saragovi

McGill University, Montreal, Canada

Neurotrophins are growth factors implicated in neuronal development, maintenance, and health. NGF binds to TrkA receptors, Neurotrophin-3 binds to TrkC receptors, and BDNF binds to TrkB receptors. All neurotrophins also bind a receptor termed p75. While the activity of Trks is associated with neuronal survival, p75 has multiple actions, but it generally activates apoptotic pathways. Each of the Trk receptors is expressed in neurons whose degeneration is etiological to disease states. For example, NGF acts upon cholinergic neurons (CNS, memory/learning) and sympathetic/sensory neurons (PNS, pain) that express TrkA. BDNF acts upon dopaminergic neurons (CNS, Parkinson's, memory, depression, schizophrenia) that express TrkB. The NGF protein has been used as a biopharmaceutical to attempt neuroprotection in Alzheimer's disease, diabetic neuropathy, and other conditions. Unfortunately the use of NGF as a therapeutic agent has been compromised by its poor pharmacokinetics, and pleiotropic effects due in part due to its binding to TrkA and p75 receptors. Thus, while the rationale of targeting TrkA (or p75) for neuroprotection is strong, pharmacological validation is still lacking because NGF is not an effective agent. As an alternative, we developed drug-like ligands of the neurotrophin receptors through "neurotrophin mimicry" and "antibody mimicry"; to develop small molecule ligands of the neurotrophin receptors. These ligands bind at the ectodomain of the receptor with high selectivity, and they have drug-like chemical properties. Binding and functional assays *ex vivo* showed activity either as agonists, as competitive antagonists, or as pure antagonists of the target receptor. Here we present a series of TrkA agonists and of p75 antagonists as neuroprotective agents *in vivo*, in acute and in chronic models of neurodegeneration. Each of these *in vivo* models represents a progressively more challenging therapeutic target. First, after optic nerve axotomy the retinal ganglion cells whose axons form the optic nerve degenerate and die at a rapid rate: 50% are lost at 1 week and 90% are lost at 2 weeks post-injury. TrkA agonists delayed the loss of RGCs: ~75% and ~50% remained viable at 1 and 2 weeks post-injury. A p75 antagonist was also neuroprotective but only for 1 week, likely reflecting the need to block p75 pro-apoptotic pathways in a chronic manner. As reported by others, NGF is not protective in this acute model. Second, in ocular hypertension (glaucoma) the retinal ganglion cells die in a chronic and progressive manner which is reminiscent of Alzheimer's disease. After 6 weeks of untreated glaucoma there is a loss of ~35% of these retinal neurons. Treatment with drugs that normalize ocular pressure reduce neuronal loss but there is a continuing progressive loss of ~20% of neurons. In this paradigm, combining a pressure-lowering drug with TrkA agonists is highly neuroprotective and reduces neuronal loss to zero. The p75 antagonists do not work, likely because a chronic condition requires the frequent use of p75 blockers. Current work is addressing higher frequency and dosing of p75 antagonists. As reported by others, NGF is not protective in this chronic model. Third, in age-associated cognitive impairment there is a linear correlation between loss of TrkA expression in cholinergic neurons, and cell atrophy/shrinkage leading to frank cell death. These events also correlate well with cognitive state and performance. Short-term delivery of a TrkA agonist was highly neuroprotective. It delayed cell shrinkage, maintained expression of cholinergic markers, and improved memory/learning for up to 3 months post-drug delivery. Currently we are testing p75 antagonists in this paradigm, and are expanding the *in vivo* model by testing the agents in a transgenic mouse model of Alzheimer's disease. Together, these results validate the targeting of Trk (and perhaps p75) receptors for the therapy of neurodegenerative disorders.



Hyman M. Schipper, MD, PhD, FRCPC, McGill University and Osta Biotechnologies, Inc.

Dr. Schipper received his MD and PhD (Neuroendocrinology) degrees at McGill University in 1982. He completed Internal Medicine Residency at the Sir Mortimer B. Davis Jewish General Hospital (McGill; 1982-4), a Residency in Neurology at Columbia University (1984-7) and a Fellowship in Endocrinology at Tufts University (1987-8). Dr. Schipper is currently tenured Professor of Neurology and Medicine (Geriatrics) at McGill University, staff neurologist at the Jewish General Hospital, and consultant at other Montreal institutions. He is founding director of the Centre for Neurotranslational Research and the Biomedical Redox Laboratory at the Jewish General Hospital. In 2005, he became founding scientist and medical director (neurosciences) of Molecular Biometrics LLC, a company developing metabolomics-based diagnostic technologies in neurodegenerative diseases and assisted reproduction. Dr. Schipper's long-standing research interests are in the fields of oxidative stress, brain aging and neurodegenerative diseases. Since 1990, his laboratory has garnered extensive evidence implicating heme oxygenase-1 (HO-1) and iron-containing astroglia in CNS senescence and free radical-related neurodegenerative disorders. Dr. Schipper has published over 140 primary and review articles on various aspects of the redox neurosciences and related topics and is an inventor on 11 patents. He serves on the editorial board of the *Journal of Neurochemistry*, is an internal examiner for the Canadian Institutes of Health Research, and is a member of 14 professional societies. At McGill University and the Jewish General Hospital, Dr. Schipper provides basic and clinical teaching in the neurosciences and coordinates an interdisciplinary course on Free Radical Biomedicine in the Faculty of Science.

Suppression of Glial HO-1 Activity as a Potential Neurotherapeutic Intervention in AD

Hyman M. Schipper, MD, PhD, FRCPC
McGill University

The mechanisms responsible for oxidative damage, pathological brain iron deposition and mitochondrial insufficiency in Alzheimer disease (AD) remain enigmatic. Heme oxygenase-1 (HO-1) is a 32 kDa stress protein that catabolizes heme to biliverdin, free iron and carbon monoxide. The *ho-1* gene is exquisitely sensitive to oxidative stress and is induced in brain and other tissues in various models of disease and trauma. Our laboratory demonstrated that 1) HO-1 protein is significantly over-expressed in AD-affected temporal cortex and hippocampus relative to neurohistologically-normal control preparations, 2) in cultured astrocytes, HO-1 up-regulation by transient transfection of the human *ho-1* gene, or stimulation of endogenous HO-1 expression by exposure to β -amyloid, TNF α or IL-1 β , promotes intracellular oxidative stress, opening of the mitochondrial permeability transition pore and accumulation of non-transferrin iron in the mitochondrial compartment, and 3) the glial iron sequestration renders co-cultured neuron-like PC12 cells prone to oxidative injury (reviewed in Schipper HM. *Ageing Res Rev* 3: 265-301, 2004). Induction of the astroglial *ho-1* gene may constitute a 'common pathway' leading to pathological brain iron deposition, intracellular oxidative damage and bioenergetic failure in AD and other human CNS disorders. **Hypothesis:** Targeted suppression of glial HO-1 hyperactivity may prove to be a rational and effective neurotherapeutic intervention in AD and related neurodegenerative disorders. To begin testing this hypothesis, studies have been initiated in collaboration with Osta Biotechnologies (Montreal) to determine whether systemic administration of a novel, selective and brain-permeable inhibitor of HO-1 activity ameliorates cognitive dysfunction and neuropathology in a transgenic mouse model of AD.



Einar Sigurdsson, PhD, New York University Langone Medical Center

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

modified A β derivatives as potential immunotherapy for Alzheimer's disease. Furthermore, they showed for the first time that active and passive immunization delayed the onset of prion disease in mice. They have now been able to prevent clinical symptoms in a large number of infected mice with a novel oral immunization approach. In addition, they published the first study showing that chelators are a potential therapy for prion disease. On the diagnostic front, Dr. Sigurdsson and colleagues published the initial report on detection of amyloid plaques in living brains by magnetic resonance imaging. Lately, he has pioneered the approach to harness the immune system to target pathological tau protein, which will be the focus of his presentation. Dr. Sigurdsson is currently supported by the NIH, the Alzheimer's Drug Discovery Foundation and the Alzheimer's Association (Zenith Fellow), and he is a recipient of the Irma T. Hirschl Career Scientist Award.

Tau-Focused Vaccine Therapy for AD and Related Tauopathies

Einar M. Sigurdsson, PhD

Departments of Physiology and Neuroscience, and Psychiatry, NYU Langone Med Ctr, New York

Immunotherapies that target the amyloid- β (A β) peptide in Alzheimer's disease (AD) have consistently resulted in A β clearance and prevented cognitive decline in mouse studies. Clinical trials using this approach were halted because of encephalitis observed in a small subset of patients but promising preliminary findings have emerged from this trial. These include reduction in A β burden and cognitive stabilization in at least some of the subjects within the reported time period, although recent findings suggest that clearance of A β plaques may not halt cognitive deterioration. Refinement of this approach is currently underway, and additional clinical trials have been initiated by several companies. Another important target in AD is the neurofibrillary tangles and their smaller assemblies, composed primarily of hyperphosphorylated tau proteins, which correlate well with the degree of dementia. Histological analysis in AD brains and mouse models indicate that A β and tau pathologies are likely synergistic. Hence, targeting both pathologies at the same time may be more effective, and is likely to be essential as early diagnosis prior to cognitive decline is currently not possible. Also, A β immunotherapy only results in a very limited indirect clearance of tau aggregates in dystrophic neurites, showing the importance of developing a separate therapy that directly targets all forms of pathological tau.

Our findings in two tangle mouse models indicate that immunization with a phospho-tau derivative reduces aggregated tau in the brain and prevents or slows progression of the tangle-related behavioral phenotype. Importantly, cognitive impairment is prevented with this type of therapy. These antibodies enter the brain and bind to pathological tau within neurons but it is conceivable that the therapeutic effect is at least in part due to clearance of extracellular tau that may have a pathological function. We are currently clarifying further the mechanism of action of our immunotherapy targeting pathological tau. In addition, we are assessing the feasibility of using our prototype tau-based immunogen(s) for clinical trials as well as determining the epitope specificity of this promising therapeutic approach.



David Vocadlo, PhD, Simon Fraser University

David Vocadlo completed his PhD in the laboratory of Prof. S.G. Withers at UBC in 2002 and his interest in fusing chemistry and biology drew him to the laboratory of Prof. C.R Bertozzi at the University of California at Berkeley where he was a CIHR Postdoctoral Fellow. In 2004 Dr. Vocadlo was appointed as an assistant professor to the Department of Chemistry at Simon Fraser University and Canada Research Chair in Chemical Glycobiology. He is a Scholar of the Michel Smith Health Research Foundation and an affiliate of the Brain Research Centre at UBC.

Selective Inhibitors for O-glycosylation Processing Enzymes: Design, Synthesis, and Effects on Tau Phosphorylation *in vivo*

David Vocadlo
Simon Fraser University

O-linked β -N-acetylglucosamine (O-GlcNAc) is an abundant post-translational modification of nucleocytoplasmic proteins including the microtubule associated protein tau. The enzyme installing this modification onto serine and threonine residues of target proteins is O-GlcNAc transferase (OGT) and the enzyme mediating its removal is O-GlcNAcase (OGA). This modification has been shown for some proteins, including tau, to be reciprocal to serine/threonine phosphorylation. Our studies on the structure and function of O-GlcNAcase and the observation that O-GlcNAc is reciprocal to phosphorylation of tau in human brain have led us to develop highly potent and selective inhibitors of this enzyme. We find some inhibitors are orally available and act to increase O-GlcNAc levels in brain while decreasing phosphorylation at pathologically-relevant phosphorylation sites. Here we describe the general background to O-GlcNAc post-translational modification and our studies leading to the design of a highly potent and selective O-GlcNAc inhibitors.



D. Martin Watterson, PhD, Northwestern University

Dr. Watterson holds the John G. Searle Endowed Chair in Molecular Biology and Biochemistry at Northwestern University and is a Professor of Molecular Pharmacology and Biological Chemistry in the Northwestern University Feinberg School of Medicine in Chicago. Dr. Watterson has published articles in peer-reviewed journals in the areas of drug discovery, signal transduction, structural biology, pharmacology and medicinal chemistry and has patent filings in the areas of novel small molecule drugs and in immunodiagnostics. He has advised major pharmaceutical and biotech companies in diverse areas of early stage discovery, served on corporate Board of Directors, and advised various American and other government agencies in science and technology development. His Ph.D. training was in the area of Biophysical Chemistry at Emory University, followed by postdoctoral training at Duke University Medical Center, where he was supported by a National Research Service Award from the National Institutes of Health (NINDS). Dr. Watterson held the positions of Assistant Professor and Associate Professor at The Rockefeller University from 1978-1982 where he was an Andrew Mellon Fellow. He later was a Howard Hughes Investigator and Professor of Pharmacology at Vanderbilt Medical Center before moving to Northwestern University, where he served as a Department chair and later founded the Drug Discovery Program. In his role as Co-Director of the University Center for Drug Discovery and Chemical Biology, Dr. Watterson facilitated the development of novel compounds emanating from Center investigators and their movement towards the clinic.

Gene-Regulating Protein Kinase Inhibitors as Potential Alzheimer's Disease Therapeutics

D. Martin Watterson, Laura K. Chico, Aaron S. Borders, Laurie K. McNamara, Linda J. Van Eldik, and Saktimayee M. Roy
Center for Drug Discovery and Chemical Biology, Northwestern University, Chicago IL

The serine/threonine protein kinase, p38 α MAPK, is an established drug discovery target for inflammation-linked peripheral disorders, such as rheumatoid arthritis. The rationale is based on the critical role that p38 α MAPK plays in the increased biosynthesis of proinflammatory cytokines and other stress-related gene products in response to disease or trauma. The stress-induced increase in cytokine levels can result in tissue injury. The goal is to find small molecules with adequate ADMET properties that allow use at the appropriate dose and therapeutic time window such that the injurious cytokine levels are restored back toward those characteristic of organismal homeostasis. Our on-going research in this area is to extend the drug discovery search to CNS injuries and diseases. Our recent public disclosure (Munoz et al., 2007, *J Neuroinflammation* 4:21) of the design approach, and results with our novel compounds in an Alzheimer's disease-relevant injury model provided an initial proof of concept. The establishment of the chemistry platform for generating novel compounds with potential for the desired pharmacokinetics and efficacy served as the foundation for intellectual property filings and indicate the feasibility of the proposed medicinal chemistry campaign. The platform and initial results will be presented.



Karl H. Weisgraber, PhD, Gladstone Institute of Neurological Disease

Dr. Weisgraber received a B.A. degree in Zoology and a Ph.D. degree in Organic Chemistry from the University of Connecticut. He has served on several Editorial Boards and NIH Study Sections and is a member of numerous professional societies. In 1994, he was awarded the Metropolitan Life Foundation Award for Medical Research. He has over 250 published articles. His long-standing research interests focus on the structure and function of apolipoprotein E (apoE). Initially, this interest centered on the role of apoE in cardiovascular disease, but has expanded in recent years to include the role of apoE, in particular the apoE4 isoform, in Alzheimer's disease. The experimental approach involves the use of x-ray crystallography, site-directed mutagenesis, and

other methods of biophysical characterization to define differences among the apoE isoforms that are responsible for the differential effects that the isoforms exert in various disease settings.

Understanding the Structural Basis for the Association of ApoE4 with Alzheimer's Disease: Opening the Door for Therapeutic Approaches

Karl H. Weisgraber
Gladstone Institute of Neurological Disease

Despite intense interest, the molecular mechanisms underlying the association of apoE4 with Alzheimer's disease are not clear. Since the function (or dysfunction) of a protein results from its structure, our focus is to determine the structural differences among the isoforms and their effects on neurodegeneration. Understanding how the structure of apoE4 impacts neurodegeneration is likely to provide insight into therapeutic approaches to blunt or reduce the effects of apoE4. ApoE4 structure and physical properties differ from apoE2 and apoE3 in two important ways: 1) Domain interaction in which the N- and C-terminal structural domains interact through a salt bridge between arginine-61 and glutamic acid-255, generating a compact tertiary structure; and 2) ApoE4 is the least stable of the isoforms to protein unfolding. Current mouse models cannot distinguish between these properties as both are expressed simultaneously. To distinguish the relative contribution of these two properties to neurodegeneration, we took advantage that mouse apoE does not display either of the apoE4 properties and generated a mouse model specific for domain interaction (introduction of arginine-61), using gene targeting. This model exhibits synaptic, functional, and cognitive deficits compared to wildtype mice, demonstrating that domain interaction contributes to neurodegeneration and establishes it as a therapeutic target. To establish proof of principle for this approach, we used *in silico* screening to identify compounds that would potentially interfere with domain interaction and convert apoE4 into an "apoE3-like molecule". Using an *in vitro* test for domain interaction, we identified several compounds that interfered with domain interaction.



Moussa B.H. Youdim, PhD, Technion-Israel Institute of Technology

Prof. Moussa Youdim was chairman of Pharmacology from its inception from 1977 to 1994. He is now the Finkelstein Professor of Life Sciences and Professor of Pharmacology at the Technion-Rappaport Family Faculty of Medicine and the Director of the Eve Topf and National Parkinson Foundation (USA) Centers of Excellence for Neurodegenerative Diseases Research and Teaching at Technion. He is internationally renowned for his research in depressive illness, Parkinson's disease and Alzheimer's disease and drug development for these disorders and for establishing the importance of monoamine oxidase and brain iron metabolism for brain function that can lead to cognitive impairments in ADHD and neurodegenerative diseases. He has received numerous major awards and honours from Israel, U.S., England, Germany, Iran, Denmark, Holland and Switzerland, including two Honorary Doctorate of Philosophy, Honoris Causa,

from universities of Semmelweis University (Hungary) and Pisa (Italy). From 1991 through 1999, he was a Fogarty International Scholar-in-Residence at the Fogarty International Center for Advanced Study in the Human Health Sciences program of the National Institute of Health in Bethesda, USA, the Only Technion academic to receive this honor.

Novel Therapeutic Approaches Constituting Multimodal Drugs for Alzheimer's Disease

Moussa B.H. Youdim

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Novel therapeutic approaches for the treatment of Alzheimer's disease (AD) comprise drug candidates designed specifically to act on multiple CNS targets. One major pathology of AD is the accumulation of iron in nucleus basalis, dentate gyrus, amyloid plaques, and tangles. The iron is thought to contribute the onset of oxidative stress and glutaminergic excitotoxicity. We have synthesized several multifunctional non-toxic, brain permeable iron chelator drugs, M-30 series, possessing propargyl monoamine oxidase (MAO) inhibitory moiety, with neuroprotective and neurorestorative activities and iron-chelating moieties, from our prototype iron chelator VK-28. M-30 and its derivatives were shown to possess a wide range of pharmacological activities, including pro-survival neurorescue effects, induction of neuronal differentiation and regulation of amyloid precursor protein (APP) and β -amyloid ($A\beta$) levels. M-30 was found to decrease apoptosis of SH-SY5Y neuroblastoma cells in a neurorescue serum deprivation model, via reduction of the pro-apoptotic proteins Bad and Bax, and inhibition of the apoptosis-associated phosphorylated H2A.X protein (Ser 139) and caspase 3 activation. In addition, M-30 and its derivative induced the outgrowth of neurites, triggered cell cycle arrest in G0/G1 phase and enhanced the expression of growth associated protein-43, HIF (Hypoxia Inducing Factor) and the neurotrophin, erythropoietin. This has been shown to be associated with the inhibition of iron dependent prolyl-4-hydroxylase that regulates HIF. These compounds have the ability of converting more than 85% of adult human stem cells in culture into neurons. Furthermore, since APP has been shown to be an iron regulated protein, similar to ferritin, by possessing 5' UTR in its mRNA element, M-30 and its derivatives markedly reduced the levels of cellular APP and β -C-terminal fragment (β -CTF) and the levels of the amyloidogenic $A\beta$ peptide in the medium of SH-SY5Y cells and Chinese hamster ovary cells stably transfected with the APP 'Swedish' mutation. As a consequence levels of the non-amyloidogenic soluble APP α and α -CTF in the medium and cell lysate respectively were coordinately increased. These properties, together with their cholinesterase and brain selective MAO inhibitory activities and propargylamine dependent neuroprotective and neurorestorative effects, suggest that these drugs might serve as an ideal drug for AD without resorting to inhibition of β -secretase, in which oxidative stress and iron dysregulation have been implicated.

2009 DRUG DISCOVERY FOR NEURODEGENERATION

WASHINGTON, DC • FEBRUARY 2-3, 2009

The purpose of the conference is to advance drug discovery for neurodegenerative disease by educating academic scientists on the processes of translating basic research into novel therapies. The conference will give participants knowledge and relevant resources about this field of scientific investigation; and address the associated barriers and challenges.

Speakers and chairs will present lectures and case studies on: **Alzheimer's disease, Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis and Multiple Sclerosis.** Ample time for questions and networking is also integrated into the program.

SESSIONS

- I. Basics of Medicinal Chemistry
- II. Hits & Leads: Early Phases of Drug Discovery
- III. Pre-Clinical Proof-of-Concept and Development
- IV. Issues in Technology Transfer: Interactions and Intellectual Property
- V. Ask the Experts: Drug Discovery for Neurodegenerative Disease
- VI. Resources and Services for Advancing Drug Discovery

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

1. To train a cadre of interdisciplinary scientists in the principles of drug discovery for neurodegenerative disease.
2. To provide a platform for scientists to exchange ideas, knowledge and resources about drug discovery for neurodegenerative disease.
3. To stimulate pre-clinical research in the discovery and testing of novel compounds aimed at the prevention and treatment of neurodegenerative disease.
4. To build public-private partnerships that will accelerate drug discovery for neurodegenerative disease.
5. To publish the conference proceedings in an open-access scientific journal available on PubMed.
6. To provide Continuing Medical Education (CME) credits.

