

# DRUG DISCOVERY FOR NEURODEGENERATION CONFERENCE

Washington, DC • February 2-3, 2009

Presented by the Alzheimer's Drug Discovery Foundation



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# TABLE OF CONTENTS

WELCOME	4
ABOUT ADDF	5
PROGRAM	6
SUPPORTERS, EXHIBITORS, PARTNERS	8
ADDF YOUNG INVESTIGATOR AWARDS AND SCHOLARSHIPS	11
CHAIRS, SPEAKERS, PANELISTS – BIOS AND PRESENTATIONS	12

Thomas M. Argentieri	29
William A. Banks	25
Louis P. Berneman	34
Lucie Bruijn	48
Daniela Brunner	27
P. Jeffrey Conn	39
Kathleen A. Denis	32
Howard Fillit	13
Marcie Glicksman	21
Antony Horton	48
Cynthia Joyce	48
Alan Kozikowski	15
Christopher Lipinski	19
Frank M. Longo	17
Fred D. Lublin	42
Suzana Petanceska	30
Lorenzo Refolo	45
Jeffrey Rothstein	41
Colin G. Sandercock	33
Todd Sherer	37
Richard B. Silverman	16
Edward G. Spack	28
Karen L. Steinmetz	23
John S. Swartley	35
Jordan Tang	18
Leticia M. Toledo-Sherman	40
Katherine Tsaioun	44
Linda Van Eldik	22
D. Martin Watterson	46
Nancy G. Wehner	26



## Mission

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

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

ADDF has an impressive track record of selecting and supporting excellent AD drug discovery research. Our scientists have created entirely new classes of drugs in development for AD, screened millions of compounds, identified hundreds of leads, executed tens of patents and licenses, and have advanced compounds into clinical trials. To date, we have awarded over \$33M for more than 240 research programs and conferences worldwide.

## Our Annual Conferences

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

Our Annual *International Conference for Alzheimer's Disease Drug Discovery*, held in October, focuses on the discovery and development of drugs targeting Alzheimer's disease and related dementias. The *Drug Discovery for Neurodegeneration* conference, held in February, is designed to educate scientists on the process of translating basic neuroscience research into innovative therapies. ADDF also plans smaller "catalyst conferences" that center around a relevant topic in the field of neurodegeneration.

If you would like additional information about any of ADDF's conferences, please contact Filomena Machleder, Assistant Director for Institutional Partnerships, at +1. 212.901.8004 or [fmachleder@alzdiscovery.org](mailto:fmachleder@alzdiscovery.org).

# Welcome Notes



On behalf of the Alzheimer's Drug Discovery Foundation (ADDF), I am pleased to welcome you to the 3<sup>rd</sup> Drug Discovery for Neurodegeneration Conference!

The conference will advance the development of new drugs by educating academic and biotech scientists on the principles of drug discovery for neurodegenerative diseases, including issues such as target validation, lead discovery, pre-clinical proof-of-concept and HTS. The conference will also give participants knowledge and relevant resources about this field of scientific investigation and address the associated barriers and challenges.

The conference aims are:

- To train a cadre of interdisciplinary scientists in the principles of drug discovery for neurodegenerative disease.
- To provide a platform for scientists to exchange ideas, knowledge and resources about drug discovery for neurodegenerative disease.
- To stimulate pre-clinical research in the discovery and testing of novel compounds aimed at the prevention and treatment of neurodegenerative disease.

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of PESI, LLC and Alzheimer's Drug Discovery Foundation (PESI, LLC is accredited by the ACCME to provide continuing medical education for physicians). The presentations will be archived as on-demand webcast and a post-meeting report will be published.

This conference is made possible through grant U13-AG031125 from the National Institute on Aging, the National Institute for Neurological Disorders and Stroke and the National Institutes of Health's Office of Rare Diseases. In addition, we are most grateful for the generous support of the following organizations: Eli Lilly and Company, CoMentis, sanofi-aventis, the Michael J. Fox Foundation for Parkinson's Research and Biogen Idec. Our thanks also go to our exhibitors: Apredica, Elsevier, Mouse Specifics, Pharmidex and our media partners: Karger, the New York Academy of Sciences, International Rett Syndrome Foundation, IOS Press, National Organization for Rare Disorders and the Children's Tumor Foundation. Finally, I would like to extend my personal thanks to all chairs and speakers for investing their time and energy into bringing today's event to fruition, as well as to ADDF staff for ensuring the proper support and coordination.

Please use the attached evaluation form to provide us with your feedback on this conference's format, content and presentations. These responses will help us assess this meeting's deliverables and allow us to respond even better to the future needs of our drug discovery scientific community.

Thank you for joining us and, once more, welcome to the 3<sup>rd</sup> Drug Discovery for Neurodegeneration Conference!

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

# PROGRAM

## February 1, 2009

6:00–7:00 pm	<b>On-Site Registration</b>
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## February 2, 2009

7:45 – 8:30 am	<b>Registration &amp; Continental Breakfast</b>
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8:30 – 8:35	<b>Welcome &amp; Opening Remarks</b> - Howard Fillit, MD, Executive Director, Alzheimer's Drug Discovery Foundation
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8:35 – 9:00	<b>Plenary Talk: Overview of Drug Discovery for Neurodegenerative Disease</b> - Howard Fillit, MD, ADDF
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### I. Basics of Medicinal Chemistry Chair: D. Martin Watterson, PhD, Northwestern University

9:00 – 9:10	<b>Session Overview – D. Martin Watterson, PhD</b>
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9:10 – 9:30	<b>Fundamentals of Medicinal Chemistry Refinement for CNS Compounds</b> - Alan P. Kozikowski, PhD, University of Illinois at Chicago
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9:30 – 9:40	Q&A
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9:40 – 10:00	<b>Rational Design and Medicinal Chemistry Refinement for Biosynthetic Enzymes</b> - Richard B. Silverman, PhD, Northwestern University
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10:00 – 10:10	Q&A
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10:10 – 10:25	BREAK
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10:25 – 10:45	<b>Ligand Development for Growth Factor Receptors</b> - Frank M. Longo, MD, PhD, Stanford University
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10:45 – 10:55	Q&A
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10:55 – 11:15	<b>Secretase Inhibitors: From Inhibitors towards CNS Drugs</b> - Jordan Tang, PhD, Oklahoma Medical Research Foundation
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11:15 – 11:25	Q&A
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11:25 – 11:45	<b>Hits to Leads to Drugs: What Makes a Chemical a Drug</b> - Christopher Lipinski, PhD, Melior Discovery, Inc.
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11:45 – 11:55	Q&A
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11:55 am – 1:00 pm	LUNCH
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### II. Hits & Leads: Early Phases of Drug Discovery Chair: Marcie Glicksman, PhD, Harvard NeuroDiscovery Center

1:00 – 1:10	<b>Session Overview – Marcie Glicksman, PhD</b>
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1:10 – 1:30	<b>Developing Relevant High-Throughput Assays for the Identification of Potential Drug Candidates</b> - Marcie Glicksman, PhD, Harvard University
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1:30 – 1:40	Q&A
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1:40 – 2:00	<b>Role of In Vitro Models in Drug Discovery for Neurodegenerative Disease</b> - Linda Van Eldik, PhD, Northwestern University
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2:00 – 2:10	Q&A
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2:10 – 2:30	<b>In Vitro Toxicity Testing: What, Why &amp; How</b> - Karen L. Steinmetz, PhD, DABT, SRI International
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2:30 – 2:40	Q&A
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2:40 – 2:55	BREAK
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### III. Pre-Clinical Proof-of-Concept & Development Chair: Edward G. Spack, PhD, SRI International

2:55 – 3:05	<b>Session Overview – Edward G. Spack, PhD</b>
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3:05 – 3:25	<b>Characteristics of Compounds that Cross the Blood Brain Barrier</b> - William A. Banks, MD, Saint Louis University School of Medicine
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3:25 – 3:35	Q&A
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3:35 – 3:55	<b>Requirements for a Lead Compound to Become a Clinical Candidate</b> - Nancy G. Wehner, PhD, Elan Pharmaceuticals
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3:55 – 4:05	Q&A
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4:05 – 4:25	<b>Behavioral Testing in Neurodegenerative Disease</b> - Daniela Brunner, PhD, PsychoGenics
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4:25 – 4:35	Q&A
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4:35 – 4:55	<b>The Basics of Pre-Clinical Development</b> - Edward G. Spack, PhD, SRI International
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4:55 – 5:05	Q&A
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5:05 – 5:25	<b>What Companies Look for in a Partner</b> – Thomas M. Argentieri, PhD, Wyeth Pharmaceuticals
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5:25 – 5:35	Q&A
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5:35 – 5:45	<b>Closing Remarks</b> - Howard Fillit, MD, Executive Director, Alzheimer's Drug Discovery Foundation
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5:40 – 7:00	<b>NETWORKING RECEPTION</b>
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## February 3, 2009

8:00 – 8:30 am	<b>Continental Breakfast</b>
8:30 – 8:40	<b>Welcome &amp; Opening Remarks</b> - Suzana Petanceska, PhD, National Institute on Aging
<b>IV. Issues in Technology Transfer: Interactions and Intellectual Property</b> <b>Chair: Kathleen A. Denis, PhD, Rockefeller University</b>	
8:40 – 8:45	<b>Session Overview – Kathleen A. Denis, PhD</b>
8:45 – 9:15	<b>Working Effectively with Your TTO: Roles and Responsibilities</b> - Kathleen A. Denis, PhD, Rockefeller University
9:15 – 9:25	Q&A
9:25 – 9:55	<b>Intellectual Property 101: A Primer For Investigators</b> - Colin G. Sandercock, Proskauer Rose LLP
9:55 – 10:05	Q&A
10:05 – 10:35	<b>Creating Relationships with Industry: Consulting, Research, MTA's and Patent Licensing</b> - Louis P. Berneman, PhD, Texelerate
10:35 – 10:45	Q&A
10:55 – 11:15	<b>Should You Start a Biotechnology Company?</b> - John S. Swartley, PhD, University of Pennsylvania
11:15 – 11:25	Q&A
11:25 – 11:35	BREAK
<b>V. Ask the Experts: Drug Discovery for Neurodegenerative Disease</b> <b>Chair: Todd Sherer, PhD, Michael J. Fox Foundation for Parkinson's Research</b>	
11:35 – 11:40	<b>Breakout Session Overview – Todd Sherer, PhD</b>
11:40 am – 12:50 pm	<b>Alzheimer's Disease</b> - Frank M. Longo, MD, PhD, Stanford University
	<b>Parkinson's Disease</b> - P. Jeffrey Conn, PhD, Vanderbilt University
	<b>Huntington's Disease</b> - Leticia M. Toledo-Sherman, PhD, CHDI Foundation
	<b>Amyotrophic Lateral Sclerosis</b> - Jeffrey Rothstein, MD, PhD, Johns Hopkins University
	<b>Progressive Multiple Sclerosis</b> - Fred D. Lublin, MD, Mount Sinai School of Medicine
12:50 – 1:50	LUNCH
<b>VI. Resources and Services For Advancing Drug Discovery</b> <b>Chair: Lorenzo Refolo, PhD, National Institutes of Health/National Institute of Neurological Disorders and Stroke</b>	
1:50 – 2:00	<b>Session Overview – Lorenzo Refolo, PhD</b>
2:00 – 2:20	<b>ADDME - Avoiding Drug Development Mistakes Early</b> - Katya Tsaion, PhD, Aprelica
2:20 – 2:30	Q&A
2:30 – 2:50	<b>Resources at the National Institute of Health – Suzana Petanceska, PhD, National Institute on Aging and Lorenzo Refolo, PhD, National Institute of Neurological Disorders and Stroke</b>
2:50 – 3:00	Q&A
3:00 – 3:20	<b>Academic Models of Drug Discovery Services</b> - D. Martin Watterson, PhD, Northwestern University
3:20 – 3:30	Q&A
3:30 – 4:00	<b>Foundation Resources Panel</b> Chair: Howard Fillit, MD, Alzheimer's Drug Discovery Foundation  Panelists: Lucie Bruijn, PhD, ALS Association Antony Horton, PhD, International Rett Syndrome Foundation Cynthia Joyce, SMA Foundation Todd Sherer, PhD, Michael J. Fox Foundation for Parkinson's Research Leticia M. Toledo-Sherman, PhD, CHDI Foundation
4:00 – 4:10	Q&A
4:10 – 4:20	<b>Closing Remarks</b> - Howard Fillit, MD, Alzheimer's Drug Discovery Foundation

# SPONSORS, EXHIBITORS AND MEDIA PARTNERS

The conference is supported by conference grant **U13-AG031125** from the **National Institute on Aging**, the **National Institute for Neurological Disorders and Stroke** and the **National Institutes of Health's Office of Rare Diseases**.

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salutes this important conference to advance drug discovery for orphan neurological diseases.

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# 2009 ADDF YOUNG INVESTIGATOR AWARDS and SCHOLARSHIPS

Congratulations to all the winners of the 2009 Outstanding Young Investigator Awards and the ADDF Young Investigator Scholarships! These highly prestigious Awards and Scholarships recognize the early achievements of talented young investigators and seek to encourage the career development of the next generation of research scientists.

## ADDF OUTSTANDING YOUNG INVESTIGATOR AWARDS

*The 2009 ADDF Young Investigator Awards are presented to:*

David Butler  
Jessica Langbaum  
Emma Mendonca  
Vishakantha Murthy  
Usha Narayan

## ADDF YOUNG INVESTIGATOR SCHOLARSHIPS

*The winners of the 2009 ADDF Young Investigator Scholarships are:*

Mabel Abraham  
Sabah Ansar  
Shreaya Chakroborty  
Andrea Cronican  
Fan Ding  
Amos Fatokun  
Nicholas Fitz  
Avi Friedlich  
Rima Hajjo  
Ryan T. L. Hamilton  
Yuan-Shih Hu  
Maria Jimenez-Sanchez  
Suresh Kumar  
Hyun Pil Lee  
Tao Ma  
Zane Martin  
Heather Menchen  
Bradley Miller  
Fozia Mir  
Boobalan Pachaiyappan  
Tristano Pancani  
Sharotka Simon  
Kai-Hui Sun  
Hao Tang  
Yongjie Yang

**CHAIRS, SPEAKERS, PANELISTS  
BIOS AND ABSTRACTS**



## **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.

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### **An Overview of Drug Discovery for Neurodegenerative Disease**

The scope of discovery, development and delivery of a drug for neurodegenerative disease is often under-appreciated by those who have not been directly involved in pre-clinical research or clinical development. Success in this field requires an extremely broad and coordinated multidisciplinary effort. Impediments to success can arise from a large number of sources. A discussion of these challenges within a context of current targets for treating neurodegenerative diseases will be presented.

## Session I. Basics of Medicinal Chemistry

*Chair – D. Martin Watterson, PhD, Northwestern University*

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This session will focus on the fundamentals of drug discovery chemistry and how this is driven by later-stage considerations of pharmacokinetics, pathophysiology and production. Introductory lectures will address what physical and biological features make a chemical scaffold or small molecule “drug-like”, and the potential impact of considering such properties on selection of compound libraries for screening and the follow-up medicinal chemistry refinement. The lectures will also introduce key concepts of medicinal chemistry refinement, with emphasis on CNS drug discovery, used in taking a screening hit into a lead compound and, eventually, into selection of a candidate for drug development. These introductory lectures will be followed by three case studies representing different classes of single molecular CNS targets that will demonstrate the application of these principles to project design and management. At the end of this session, participants should have familiarity with key concepts that are used in small molecule compound selection, and understand the general processes involved in medicinal chemistry refinement in early stage CNS drug discovery.

### **Session Overview – D. Martin Watterson, PhD**

#### **Fundamentals of Medicinal Chemistry Refinement for CNS Compounds**

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

#### **Rational Design and Medicinal Chemistry Refinement for Biosynthetic Enzymes**

Richard B. Silverman, PhD, Northwestern University

#### **Ligand Development for Growth Factor Receptors**

Frank M. Longo, MD, PhD, Stanford University

#### **Secretase Inhibitors: From Inhibitors towards CNS Drugs**

Jordan Tang, PhD, Oklahoma Medical Research Foundation

#### **Hits to Leads to Drugs: What Makes a Chemical a Drug**

Christopher Lipinski, PhD, Melior Discovery, Inc.



**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.

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## Fundamentals of CNS Drug Discovery – From Bench to the Beside in Academia

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. A variety of epigenetic enzymes have now been shown to participate in the control of gene silencing and gene activation. In our efforts to identify HDACIs that 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 general lack of enzyme selectivity. To properly address the design of new isozyme selective HDACIs, one must elucidate the contribution that each of the regions of these molecules makes to selectivity. We have 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 of their catalytic gorge regions, as well as to more broadly assess the effect of variations in the zinc binding groups. As is relevant to any serious drug discovery undertaking, significant attention must be devoted to a compound's druggability including its metabolic stability and its ability to penetrate the blood brain barrier. 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.

While HDAC6 selective compounds provide one route forward to new therapies for neurodegenerative diseases, we have also been exploring the chemistry and biology of Glycogen Synthase Kinase 3 (GSK-3) inhibitors. GSK-3 is a serine-threonine kinase originally found to regulate glycogen metabolism. Later, it was established that GSK-3 affects a variety of biological processes such as cell cycle progression, proliferation, apoptosis, signaling, and transcription by phosphorylation of many different substrates. In mammals, GSK-3 consists of two distinct isoforms,  $\alpha$  and  $\beta$ , which are highly homologous within their ATP binding domain, whereas they are significantly different in their terminal regions. GSK-3 $\beta$  is one of the kinases involved in the hyperphosphorylation of tau, a microtubule [MT] binding protein. Tau hyperphosphorylation is known to result in MT destabilization, leading to disruption of axonal function, and eventual degeneration of nerve terminals. GSK-3 $\beta$  is thus a potential therapeutic target for the treatment of neurodegenerative disease and particularly tauopathies. The synthesis and biological evaluation of novel GSK-3 inhibitors created from an initial HTS hit will be summarized.



## **Richard B. Silverman, PhD, Northwestern University**

Professor Silverman received his B.S. degree in chemistry from The Pennsylvania State University in 1968 and his Ph.D. degree in organic chemistry from Harvard University in 1974 (with time off for a two-year military obligation from 1969-1971). After two years as a NIH postdoctoral fellow in the laboratory of the late Professor Robert Abeles in the Graduate Department of Biochemistry at Brandeis University, he joined the chemistry faculty at Northwestern University. In 1986 he became Professor of Chemistry and Professor of Biochemistry, Molecular Biology, and Cell Biology. In 1996 he was named the Arthur Andersen Professor of Chemistry for a period of two years, in 2001 he became the Charles Deering McCormick Professor of Teaching Excellence for three years, and in the fall of 2004 he was named the John Evans Professor of Chemistry for an indefinite period of time. His awards include a DuPont Young Faculty Fellowship in 1976, an Alfred P. Sloan Research Fellowship in 1981-1985, a NIH Research Career Development Award 1982-1987, being named a Fellow of the American Institute of Chemists in 1985 and a Fellow of the American Association for the Advancement of Science in 1990, and recipient of an Arthur C. Cope Senior Scholar Award from the American Chemical Society in 2003. He is the recipient of several teaching awards, including the E. LeRoy Hall Award for Teaching Excellence and the Excellence in Chemistry Education Award from the Northwestern University Chapter of Alpha Chi Sigma Chemistry Fraternity in 1999, the Northwestern University Alumni Teaching Award in 2000, and the Charles Deering McCormick Chair in Teaching Excellence in 2001. Silverman is the inventor of Lyrica™ (pregabalin), marketed worldwide by Pfizer for refractory epilepsy, neuropathic pain, fibromyalgia, and (in Europe) for generalized anxiety disorder. He has published 240 research articles, holds 38 domestic and foreign patents, and has written four books (one translated into German).

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### **Rational Design and Medicinal Chemistry Refinement for Biosynthetic Enzymes**

#### **Design of Selective Neuronal Nitric Oxide Synthase Inhibitors for the Treatment and Prevention of Neurodegenerative Diseases**

Nitric oxide (NO) is a ubiquitous biological messenger involved in a variety of physiological processes that acts as a signal transducer but also exerts a variety of regulatory and cytostatic functions. Nitric oxide synthase (NOS) is a family of homodimeric enzymes that catalyzes the oxidation of *L*-arginine to *L*-citrulline and nitric oxide in a NADPH- and O<sub>2</sub>-dependent process. The constitutive endothelial isozyme (eNOS) is involved in the regulation of smooth muscle relaxation and blood pressure and in the inhibition of platelet aggregation. A second constitutive isozyme is neuronal NOS (nNOS), which is important for neurotransmission. A third isozyme is the inducible NOS (iNOS), which is located in activated macrophage cells and acts as a cytotoxic agent in normal immune responses.

The use of NOS inhibitors in pathologically elevated synthesis of NO has great therapeutic potential. NO overproduction by nNOS has been associated with neurodegeneration during stroke, spinal transmission of pain, migraine headaches, Parkinson's disease, Alzheimer's disease, Huntington's disease, and cerebral palsy. Compounds that inhibit nNOS would decrease the production of NO in the brain. However, because of the importance of NO to physiological functioning, potent as well as nNOS-selective inhibitors are essential.

This lecture describes the design of the first class of potent and highly dual-selective nNOS inhibitors and their modification for enhanced potency, selectivity, and lipophilicity. After the first selective inhibitors were obtained, X-ray crystallography and computer modeling guided additional modifications, and *de novo* structure-based design led to a new class of potent and selective nNOS inhibitors. Results of animal testing of some of these compounds for cerebral palsy will be described.



## Frank M. Longo, MD, PhD, Stanford University

Dr. Longo received his MD in 1981 and PhD in Neurosciences in 1983 from the University of California, San Diego. Following an internship in medicine at NYU/VA, he trained as a resident in neurology and fellow in neurobiology at University of California, San Francisco. While at UCSF he created the Neurogenetics Clinic which was the first West Coast site in the U.S. to offer DNA testing for families with Huntington's disease. He also led the creation of a national referral center for deep brain stimulation for Parkinson's disease and contributed to the development of programs in dementia, epilepsy and other areas.

At UCSF, Dr. Longo 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.

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### Ligand Development for Growth Factor Receptors

Frank M. Longo, MD, PhD<sup>1,2</sup> and Stephen M. Massa, MD, PhD<sup>3</sup>

<sup>1</sup>Department of Neurology and Neurological Sciences, Stanford University

<sup>2</sup>Department of Neurology, University of North Carolina (previous department)

<sup>3</sup>Department of Neurology, SF VA and UC San Francisco.

The p75 neurotrophin receptor (p75<sup>NTR</sup>) is expressed by the majority of neurons affected in Alzheimer's disease (AD), binds amyloid beta (A $\beta$ ) and is likely up-regulated in AD. Applying *in silico* screening and medicinal chemistry, we have developed several generations of first-in-class small molecule, non-peptide p75<sup>NTR</sup> ligands that activate survival signaling and inhibit degenerative signaling mechanisms. Small molecule p75<sup>NTR</sup> ligands inhibit A $\beta$  oligomer-induced neuritic dystrophy and death of cultured CNS neurons and death of pyramidal neurons in hippocampal slice cultures. These ligands also inhibit A $\beta$ -induced activation of multiple deleterious signaling pathways potentially contributing to AD pathology and synaptic dysfunction; block A $\beta$ -induced tau phosphorylation and prevent A $\beta$ -induced inactivation of AKT and CREB. Consistent with these signaling studies, hippocampal slice/LTP studies performed in collaboration with Dr. Ottavio Arancio at Columbia University, show that compounds block LTP impairment triggered by exogenous A $\beta$ , and restore LTP in hippocampal slices derived from mutant PS1/APP transgenic mice. *In vivo* studies demonstrate favorable drug development profiles. Preclinical studies demonstrate the ability to reverse basal forebrain cholinergic neuron atrophy and degeneration of cholinergic neurites in wild-type aged mice. Studies in AD mouse models show that ligands can reduce a number of pathological morphological endpoints and reverse a well established measure of cognitive impairment. 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). Dr. Longo is a founder and equity holder in Pharmatrophix Inc., a company focused on the development of small molecule neurotrophin receptor ligands.



**Jordan Tang, PhD**, Oklahoma Medical Research Foundation/  
University of Oklahoma Health Sciences Center

The research interest of Dr. Tang was for many years in the structure and biological function of proteases. In 1999, his laboratory cloned memapsin 2, identified it to be beta-secretase and have since studied the regulation mechanism of memapsin 2 and worked in the development of memapsin 2 inhibitor as a drug to treat Alzheimer's disease. In 2000, Dr. Tang and coworkers reported the design of first potent inhibitor for memapsin 2 and determined the crystal structure of memapsin 2 bound to this inhibitor. These developments have permitted the use of structure-based design to develop new generations of potent and selective memapsin 2 inhibitors. Significant progress in drug development of this inhibitor has been done in CoMentis, a biotech/pharmaceutical company founded by Dr. Tang and his collaborator, Dr. Arun Ghosh. The newest generation of memapsin 2 inhibitor, CTS-21166, is currently in a phase I clinical trial. For his research in memapsin 2, Dr. Tang received the Pioneer Award in 2000 from the American Alzheimer's Association.

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### **Memapsin 2 Inhibitors: Toward a Drug Candidate**

Amyloid reduction is an attractive therapeutic approach for Alzheimer disease and the inhibition of memapsin 2 ( $\beta$ -secretase, BACE1), the aspartic protease that initiates the processing of APP leading to the production of  $A\beta$ , has emerged as a major area for developing inhibitor drugs. Here, we discuss various strategy applied in the evolution of memapsin 2 inhibitors into a drug candidate. A successful drug candidate for memapsin 2 is likely to be a mimic to the catalytic transition-state. It needs to be potent with  $K_i$  near low nM range, size small enough to penetrate the blood-brain-barrier, selective vs. other human aspartic proteases and processes good drug properties. The first potent memapsin 2 inhibitor, OM99-2 (892 Da;  $K_i = 1.6$  nM), contained eight residues with the scissile bond substituted by a hydroxyethylene transition-state isostere. To facilitate the use of structure-based evolution of inhibitor structure, we determined the crystal structure of the catalytic domain of memapsin 2 bound to OM99-2. For the reduction of inhibitor size, the loss of potency from the removal of outside residues P4, P3' and P4' was compensated by the increase in protein-ligand interaction of central residues from P3 to P2'. Structural modules discovered for selectivity and potency were incorporated into new inhibitors. The path of inhibitor structural evolution was guided by data from enzyme kinetics and  $A\beta$  inhibition in cells and mice. This process has produced some inhibitors in 600s Da range with good drug-like properties. Inhibitor GRL-8234,  $K_i$  of 1.2 nM and cellular  $IC_{50}$  of about 1 nM, has good selectivity vs. cathepsin D and memapsin 1 and brain penetration of about 4%. Oral administration of GRL-8234 at 50 mg/Kg reduced  $A\beta$  by about 60% in the plasma and about interstitial  $A\beta$  by over 50% in the brain of Tg2576 mice. Continuous delivery of GRL-8234 in Tg2576 for about 3 months produced significant difference in cognitive performance over the control mice in Morris Water Maze in both escape latency and annulus crossing index (ACI). The improvement of the latter was at a level that suggested the rescue of nearly all age-related cognitive decline. An advance inhibitor, CMT-21166, has been tested in Phase I clinical trial. These development suggests that the significant progress has been made in the development of memapsin 2 inhibitors toward a drug candidate and the future of this line of drug development for an AD drug appears encouraging.



## **Christopher Lipinski, PhD, Melior Discovery, Inc.**

Dr. Christopher Lipinski was Adjunct Senior Research Fellow at the Pfizer Global R&D Groton CT Laboratories following his retirement in June 2002 and is now a Scientific Advisor to Melior Discovery, a drug repurposing startup. He is a member of the American Chemical Society (ACS), the American Association of Pharmaceutical Scientists, the Society for Biomolecular Sciences (SBS) and the European Federation for Pharmaceutical Sciences. A consultant on drug-like properties he serves on numerous scientific advisory and journal editorial boards and on the SAB's of not for profit and academic drug discovery organizations. He is the author of the "rule of five" a widely used filter to select for acceptable drug oral absorption and is a member of the ACS "Medicinal Chemistry Hall of Fame". In 2006 he received an honorary law degree from the University of Dundee and is also the 2006 SBS Achievement Award winner. In 2005 he was the ACS winner of the E. B. Hershberg Award for Important Discoveries in Medicinally Active Substances and in 2004 the winner of the Division of Medicinal Chemistry Award of the ACS Division of Medicinal Chemistry. He is an adjunct faculty member at the University of Massachusetts Amherst, and has over 225 publications and invited presentations and 17 issued US patents.

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### **Hits to Leads to Drugs: What Makes a Chemical a Drug**

Drug discovery is a highly specialized multidisciplinary effort that converts a chemical into a useful drug in human medicine. Most of chemistry space is absolutely worthless for drug discovery and is not drug-like, especially for oral drugs. Drug discovery is not chemical biology, which is the use of small molecules as tools or probes to elucidate biological pathways. Drug discovery requires good quality chemistry structures. Compounds with reactive functionality are of no value. Good quality chemical structures for drug discovery screening are much more expensive than those for chemical biology. Typically less than 15% of commercially available compounds are suitable for drug discovery screening. Good targets require chemistry / biology cooperation in target choice. Targets can be beautiful in biology but horrible in chemistry. In-vitro optimization is the easy and predictable part of drug discovery. Solving issues in Absorption Distribution Metabolism Excretion and Toxicity (ADMET) is the hard part. There is a new chemistry drug discovery paradigm called "hit to lead" that now comes before "lead optimization". Hit to lead is doing early chemistry efficiently to see if the chemistry credentials are good enough to go on to the more expensive, more labor intensive chemistry lead optimization. CNS drug discovery is special requiring extra filters and effort to get a drug into the CNS and many combinatorial chemistry libraries just do not have what it takes to make a CNS active drug.

## Session II. Hits & Leads: Early Phases of Drug Discovery

*Chair – Marcie Glicksman, PhD, Harvard NeuroDiscovery Center*

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A key component of the development of new therapeutic agents is the identification of molecules that can serve as initial lead structures on which drug discovery programs can be built. High-throughput screening of large collections of drug-like molecules for modulatory activity in disease-relevant assays is an important means to discovering these lead molecules. This session will first address strategies for the development of assays that are suitable for high-throughput screening and then strategies for secondary assays to validate the primary screening results. Most drug development efforts fail due to toxicity and ADME (absorption, distribution, metabolism and excretion) properties. This session will end with a presentation on technology used for *in vitro* toxicity and ADME testing.

### **Session Overview – Marcie Glicksman, PhD**

#### **Developing Relevant High-Throughput Assays for the Identification of Potential Drug Candidates**

Marcie Glicksman, PhD, Harvard NeuroDiscovery Center

#### **Role of In Vitro Models in Drug Discovery for Neurodegenerative Disease**

Linda Jo Van Eldik, PhD, Northwestern University

#### **In Vitro Toxicity Testing: What, Why & How**

Karen L. Steinmetz, PhD, DABT, SRI International



## **Marcie Glicksman, PhD, Harvard NeuroDiscovery Center**

Marcie Glicksman is Senior Director, Leads Discovery Group at LDDN. Dr. Glicksman has extensive experience in assay development, high throughput screening, chemical databases, animal pharmacology and preclinical development. Her bachelor's degree is from Brown University and Ph.D. from Washington University. Before joining LDDN in 2004, she had been in industry for thirteen years. Previously, she was at the start-up company, Descartes Therapeutics focused on imaging techniques. Before this, she was Director of Leads Discovery at Cubist. Before this, she was at DuPont-Merck and at Cephalon, Inc. She led the assay development and screening program for a cell-based protease project, and numerous G-protein coupled receptors, many of which were continued when Bristol Myers Squibb bought DuPont Pharmaceuticals. At Cephalon, she was co-inventor of CEP1347, a neuroprotective agent directed at a novel kinase, currently in Phase III clinical trials. She also consults for industry. She is a board member of the non-profit drug discovery organization Society for Biomolecular Screening and currently serves as the Chairman.

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### **Developing Relevant High-Throughput Assays for the Identification of Potential Drug Candidates**

There are two critical steps in the development of an assay for high throughput screening (HTS). First is the selection of the assay type that must closely model the science known about the target. This target can be an isolated enzyme or can be endogenously expressed or stably expressed in a relevant cell. Second is the optimization of the selected assay so that the small molecules that are identified are likely to be the ones of interest and with potential artifacts minimized. Included will be examples to illustrate different types of assays and the metrics and validation process for the purpose of HTS.



## **Linda Jo Van Eldik, PhD, Northwestern University**

Linda Jo Van Eldik, Ph.D., is Co-Director of the Center for Drug Discovery and Chemical Biology at Northwestern University, and is Associate Director of the Cognitive Neurology and Alzheimer's Disease Center, and Professor of Cell and Molecular Biology at the Northwestern University Feinberg School of Medicine in Chicago. Dr. Van Eldik has published peer-reviewed articles in neuroscience, glia cell biology, signal transduction, virology, and drug discovery.

Dr. Van Eldik received her Ph.D. in Microbiology/Immunology from Duke University in 1977, followed by postdoctoral training at The Rockefeller University from 1978 to 1981 where she was awarded a National Science Foundation postdoctoral fellowship and National Research Service Award in cell biology from the National Institutes of Health. She later held the positions of Assistant Professor, Associate Professor and Professor of Pharmacology and Cell Biology at Vanderbilt University School of Medicine, and was an Associate Investigator with the Howard Hughes Medical Institute before moving to Northwestern University Feinberg School of Medicine in Chicago in 1994.

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### **Role of In Vitro Models in Drug Discovery for Neurodegenerative Disease**

The development of new small molecule therapeutics for CNS disorders is a significant and expensive endeavor. Key components of the early phase of drug discovery are the identification of potentially “drugable” targets (pathways as well as single molecular targets) linked to the disease, and identification of chemical scaffolds or screening hits that can be developed into lead compounds. The increasing insight into underlying pathologic mechanisms has revealed the complexity and multiplicity of events that contribute to Alzheimer's disease pathophysiology, thereby revealing a variety of potential drug discovery targets. Once a drugable target or pathway has been selected, it is critical to develop efficient approaches for identification of appropriate chemical compounds that can serve as lead structures for further medicinal chemistry refinement and eventual selection of a candidate for drug development. This presentation will focus on strategies for secondary assays that confirm primary screening assays and help validate and prioritize which hits to move into the drug discovery pipeline.



## **Karen L. Steinmetz, PhD, DABT, SRI International**

Dr. Karen Steinmetz, PhD, DABT, has over 25 years experience in the fields of early drug discovery, safety and preclinical development in a wide variety of pharmaceutical products. She has served as Study Director on numerous GLP studies in support of regulatory applications worldwide, as Principal Investigator on NIH preclinical testing contracts including those with the National Institute on Aging and National Institute of Diabetes & Digestive & Kidney Diseases, and as the preclinical representative on industrial project teams.

Dr. Steinmetz holds a doctorate in toxicology from Indiana University. Her industrial background includes overseeing preclinical development activities and IND preparation for several San Francisco Bay Area biotechnology pharmaceutical companies.

Dr. Steinmetz' is currently the Director of the Mammalian Toxicology Program at SRI International in Menlo Park, CA.

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### **Early-Stage ADME and Toxicity Testing: What, Why & How**

Preclinical Development represents activities within a continuum linking discoveries in the lab to initiation of human clinical trials by acquiring unbiased evidence for new drug entities intended for use in humans. Preclinical studies are designed to identify a lead candidate from several 'Hits,' develop the best process for drug manufacturing, select the best formulation composition, identify potential safety liabilities, and ultimately support the intended clinical trial design. Since these parameters tend to vary between drugs and drug classes, the specific details for each preclinical development package is tailored to fit a specific application. The first step for most drugs is a general understanding of the intended clinical use including the patient profile, route, frequency, and duration of drug administration, as well as some thought on how the drug will be manufactured. Some of this information is available by knowing the disease target as well as from the efficacy screens using in vitro and in vivo models of the disease. Hits identified in the efficacy models may be tested using in vitro assays and small in vivo screens for their drug-like properties, potential indicators of toxicity, and absorption, distribution, metabolism, and excretion (ADME) properties. Before in vitro testing begins, the drug's physiochemical properties are determined, particularly solubility. ADME profiling may include microsomal metabolic stability, membrane permeability, enzyme inhibition and induction, enzyme identification and metabolite profiling, and plasma protein binding. Toxicity assays may include 'mini' Ames, hERG (iKr), and various endpoints in cultured cells to assess potential liabilities for genotoxicity, cardiotoxicity, and general toxicity, respectively. Finally, small in vivo screens assess both pharmacokinetic and toxicity parameters in the whole animal. The goal of these early assessments is to rank-order Hits for their drug-like properties and potential safety liabilities. Medicinal chemists also use this information to evaluate the impact of structural modifications or substitutions and to understand structure-activity relationships as they work to enhance a drug series. Hits having the desired ADME and toxicity profiles are moved further along the Preclinical Development continuum to enter more complex pharmacokinetic and safety studies.

## Session III. **Pre-Clinical Proof-of-Concept & Development**

*Chair – Edward G. Spack, PhD, SRI International*

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The focus of this session is the transition from lead compound to clinical testing, the scenic stretch of drug development often referred to as the “Valley of Death.” Several factors converge to kill promising compounds at this translational stage, including lack of funding/resources/expertise, the delivery challenge of the blood brain barrier and common problems of toxicity, manufacturing and formulation. Drawing on examples of past successes and failures, this series of presentations will chart the course from lead optimization to initiation of clinical testing, highlighting emerging models for internal development, outsourcing and funding. Few investigators or new companies who survive this pre-clinical phase travel the clinical path alone. Therefore the pre-clinical decisions that support or hinder partnering will also be presented.

### **Session Overview – Edward Spack, PhD**

#### **Characteristics of Compounds that Cross the Blood Brain Barrier**

William A. Banks, MD, Saint Louis University School of Medicine

#### **Requirements for a Lead Compound to Become a Clinical Candidate**

Nancy G. Wehner, PhD, Elan Pharmaceuticals

#### **Behavioral Testing in Neurodegenerative Disease**

Daniela Brunner, PhD, PsychoGenics

#### **The Basics of Pre-Clinical Development**

Edward G. Spack, PhD, SRI International

#### **What Companies Look for in a Partner**

Thomas M. Argentieri, PhD, Wyeth Pharmaceuticals



## William A. Banks, MD, Saint Louis University School of Medicine

William A Banks received his MD from University of Missouri-Columbia in 1979. He completed clinical training in Internal Medicine and later in Endocrinology and Metabolism at Tulane University and the Veteran's Affairs Medical Center-New Orleans. He was awarded a Career Development Award by the Veterans Affairs from 1982-1985 and became full professor at Tulane 1995. In 1998, he moved to the VA and Saint Louis University School of Medicine where he is currently Staff Physician and Principal Investigator (VA), Professor in the Department of Internal Medicine and the Department of Pharmacological and Physiological Sciences (SLU), and Visiting Professor of Anatomy (Showa University, Tokyo, Japan). He has published over 350 non-abstract articles, mostly related to functioning of the blood-brain barrier, and is on 10 editorial boards, including being editor-in-chief of *Current Pharmaceutical Design*. He has received numerous awards including membership in the Musser-Burch Society (Tulane's Clinical Honors Society), the VA Star Award, the 1994 University of Missouri-St. Louis Distinguished Biology Alumni Award (single award annually), the 1998 Outstanding Young Physician Award from the University of Missouri School of Medicine Medical Alumni Organization, and is the 2004 Milton D. Overholser Memorial Lecturer.

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### Characteristics of Compounds that Cross the Blood-brain Barrier

The blood-brain barrier (BBB) serves to restrict and regulate the exchange of solutes and cells between the CNS and blood. The vascular BBB is usually the focus in drug development and discovery because it provides immediate access to all regions of the brain, although the choroid plexus (blood-CSF barrier) or specialty barriers [1] can provide targeted access. Most drugs that successfully penetrate the BBB have several of the following characteristics: 1) favorable pharmacokinetics (long half-life, low volume of distribution, 2) enzymatic resistance in blood, CNS, and at the BBB, 3) absence of high affinity protein binding in blood, 4) low MW and moderately high lipid solubility, 5) a substrate for a saturable blood-to-brain transporter, 6) minimal sequestration by brain endothelial cells, 7) absence of a robust brain-to-blood transporter [2]. Principles commonly overlooked, especially in attempts to "bypass" the BBB, are 1) minimal diffusion within brain tissue, 2) minimal diffusion from CSF into periventricular tissues, 3) entry of intraventricular-injected drugs into the blood stream with the reabsorption of CSF, 4) the importance of BBB efflux systems on drug uptake and retention by the CNS, 5) competition of lipid soluble drugs by non-BBB tissues (e.g., liver) and 6) (favoring drug delivery) the low amount of drug often needed to produce a CNS effect. Many substances originally thought not to cross the BBB, including many peptides, proteins, antibodies, cytokines, and oliophosphorothioate antisense molecules, do cross by way of saturable transport systems, transmembrane diffusion, or the extracellular pathways [3;4]. Unfavorable pharmacokinetics are often as big an impediment to the therapeutic use of endogenous substances as are BBB issues. Finally, the BBB must be viewed as a dynamic, regulatory interface between the CNS and peripheral tissues that responds to developmental and physiological changes as well as to disease conditions. For this reason, drug-BBB interactions are ideally studied in disease-specific contexts [5].

[1] Neuwelt,E., Abbott,N.J., Abrey,L., Banks,W.A., Blakley,B., Davis,T., Engelhardt,B., Grammas,P., Nedergaard,M., Nutt,J., Pardgridge,W., Rosenberg,G.A., Smith,Q., & Drewes,L.R. (2008) Strategies to advance translational research into brain barriers. *Lancet Neurol.*, **7**, 84-96.

[2] Greig,N.H., Brossi,A., Pei,X.F., Ingram,D.K., & Soncrant,T.T. (1995) Designing drugs for optimal nervous system activity. In *New Concepts of a blood-brain barrier* (Greenwood,J., Begley,D.J., & Segal,M.B., eds), pp. 251-264. Plenum Press, NY

[3] Banks,W.A. (2004) Are the extracellular pathways a conduit for the delivery of therapeutics to the brain? *Current Pharmaceutical Design*, **10**, 1365-1370.

[4] Begley,D.J. (2007) Delivery of therapeutic agents to the central nervous system: the problems and the possibilities. *Pharmacology & Therapeutics*, **104**, 29-45.

[5] Banks,W.A. (2008) Editorial: The blood-brain barrier as a cause of disease. *Current Pharmaceutical Design*, **14**, 1553-1554.



## **Nancy G. Wehner, PhD**, Elan Pharmaceuticals

Dr. Wehner received her PhD degree in Immunology from the University of Minnesota (Minneapolis, MN) in 1987. Her post-doctoral fellowship was at the same institution in the Department of Chemistry. Dr. Wehner began her career in medical diagnostics research with Sanofi Diagnostics Pasteur where she specialized in assay development for autoimmune disease diagnosis. Following a move to California, she joined Anergen where she was head of Bioanalytical Assays (clinical and nonclinical support service), Quality Control, and

Pharmacology & Toxicology. While there, she was responsible for the development of monoclonal antibodies, complex biologics and vaccines for the treatment of autoimmune diseases.

Dr. Wehner currently holds the position of Vice President of Nonclinical Safety Evaluation at Elan Pharmaceuticals, South San Francisco, CA. She is responsible for pharmacology and toxicology programs in support of the development of biologic and small molecule drug products in the areas of autoimmunity and neurology.

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### **Requirements for a Lead Compound to Become a Clinical Candidate**

Lead compounds are usually selected during the screening and validation processes for primarily pharmacological attributes that make them potentially useful for a targeted indication. These compounds still require significant optimization to become an acceptable clinical candidate – they are a starting point, not an end. Lead Optimization is a process for improving efficacy and ADME properties while identifying and, where possible, minimizing toxicities. Fast and efficient optimization with early attrition of poor candidates should be the goal. This talk will look at the process of lead optimization including 1) traditional assays and methodologies for optimization, 2) new technologies being applied to optimization, 3) toxicology considerations during optimization, and 4) process tools (e.g. flow schemes) to help guide optimization.



**Daniela Brunner, PhD, PsychoGenics, Inc.**

Dr. Brunner received her Ph.D. in Experimental Psychology at Cambridge University, England and was Research Fellow of Psychiatry at Columbia University, New York State Psychiatric Institute, for many years. She has worked in mathematical models of behavior, information processing in animals and then in the characterization of genetically manipulated animal models of psychiatric and neurodegenerative disorders such as Huntington Disease (HD), schizophrenia, Wolfram Disorder, and others. As part of her work in the biotech sector, Dr. Brunner has been involved in the discovery and preclinical characterization of a drug for ADHD, currently in clinical trials, and holds patents covering highthroughput analysis of behavior for drug discovery. Dr. Brunner has worked in the last six years in the characterization of several animal models of HD, resulting in a large drug screening operation at PsychoGenics, Inc. She is particularly interested in the translation from the bench to the clinic of aspects of psychiatric and neurodegeneration pathology, in particular cognitive and psychomotor symptoms.

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### **Behavioral Testing in Neurodegenerative Disease**

Some neurodegenerative diseases have a known or suspected genetic cause, knowledge that has enabled the creation of many animal models using genetic manipulations that aim to recapitulate the core pathology. The study of behavioral and neuropathological phenotypes of the models for a specific disorder, however, has been plagued by inconsistent results across laboratories stemming from the lack of standardized husbandry and testing conditions, in addition to the intrinsic differences between the models. In one series of studies we have compared six different HD models using standardized conditions to identify the most robust phenotypic differences, best suited for preclinical therapeutic efficacy studies. With a battery of tests of sensory-motor function, such as the open field and prepulse inhibition tests, we replicate previous results showing a strong and progressive behavioral deficit in the R6/2 line (129 CAG repeats-mixed CBA/J and C57BL/6J). We present the first behavioral characterization of a new model, an R6/2 line (248 CAG-pure C57BL/6J), which also showed a progressive and robust phenotype. The BACHD line (FVB/N) showed robust and progressive deficits, while the YAC128 line (FVB/N or C57BL/6J) showed milder deficits. Finally, the HdhQ111 line (CD1) showed very mild deficits. This first extensive standardized cross-characterization of several HD animal models under standardized conditions highlights several behavioral outcomes, such as hypoactivity, amenable to standardized pre-clinical therapeutic drug screening.



## **Edward G. Spack, PhD, SRI International**

Edward G. Spack, Ph.D. is currently Senior Director, Biologics and Senior Director Business Development at SRI International in Menlo Park, California. Dr. Spack is the Senior Director of the PharmaSTART program; a consortium of SRI and four California universities (Stanford, UC Berkeley, UC San Diego and UC San Francisco) designed to chaperone discoveries from the laboratory bench to the clinic. Dr. Spack has worked in three San Francisco Bay Area biotech companies (Anergen, Valentis and InterMune) for a total of 14 years, with the bulk of his experience in the biologic drugs including humanized monoclonal antibodies, recombinant proteins and peptide vaccines. Dr. Spack has also served on the Board of Directors and the scientific advisory board of the National Myasthenia Gravis Foundation. Dr. Spack was awarded his Doctorate in Cellular Immunology at the Johns Hopkins University and held a post-doctoral fellowship at Stanford University.

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### **The Basics of Pre-Clinical Development**

Preclinical development encompasses the activities that link drug discovery in the lab to initiation of human clinical trials. The details of each preclinical development package can vary, but all have some common features. Rodent and nonrodent mammalian models are used to delineate the pharmacokinetic (PK) profile and general safety, as well as to identify toxicity patterns. One or more species may be used to determine the drug's mean residence time in the body, which depends on inherent absorption, distribution, metabolism, and excretion (ADME) properties. For drugs intended to treat Alzheimer's disease or other brain-targeted diseases, the ability of a drug to cross the blood brain barrier may be a key issue. Toxicology and safety studies identify potential target organs for adverse effects and define the Therapeutic Index (TI) to set the initial starting doses in clinical trials. Pivotal preclinical safety studies generally require regulatory oversight as defined by U.S. Food and Drug Administration (FDA) Good Laboratory Practices (GLP) and international guidelines, including the International Conference on Harmonisation (ICH). Concurrent preclinical development activities include developing the Clinical Plan (Phase 1) and preparing the new drug product including the associated documentation to meet stringent FDA Good Manufacturing Practices (GMP) regulatory guidelines. A wide range of commercial and government contract options are available for investigators seeking to advance their candidate(s). Government programs such as the Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) grants and the National Institutes of Health (NIH) Rapid Access to Interventional Development (RAID) Pilot Program provide funding and services to assist applicants in preparing the preclinical programs and documentation for their drugs. Increasingly, private foundations are also funding preclinical work. Close interaction with the FDA, including a meeting to prepare for submission of an Investigational New Drug (IND) application, is critical to ensure that the preclinical development package properly supports the planned Phase I clinical trial.



**Thomas M. Argentieri, PhD, Wyeth Pharmaceuticals**

Thomas M. Argentieri is a Senior Director in the Global Licensing and Business Development group at Wyeth Pharmaceuticals. Dr. Argentieri received his Ph.D. in Neuroscience from the University of Medicine and Dentistry in NJ in 1983. After a post-doctoral fellowship, he served on the faculty of the Department of Medicine at the University of Pennsylvania. Dr. Argentieri spent 20 years in neuroscience and cardio vascular drug discovery at Berlex and Wyeth Pharmaceuticals, and has spent the last four years in Business Development at Wyeth focused predominantly on early stage licensing opportunities. In addition to his business development responsibilities, Dr. Argentieri also serves on the editorial boards of several journals including the Journal of Pharmacology and Experimental Therapeutics, and the Open Pharmacology Journal.

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**Suzana Petanceska, PhD**, National Institutes of Health/National Institute on Aging

Dr Suzana Petanceska received a B.S. degree in molecular biology and physiology from the University of Belgrade, Yugoslavia and a Ph.D. degree in Pharmacology from New York University. Following her postdoctoral training at Rockefeller University (1995-1998) and at the Nathan Kline Institute of NYU (1998-2000) she became an Assistant Professor of Psychiatry and Pharmacology at the Nathan Kline Institute of NYU (2001-2005). Her research focused on the role of disrupted sterol metabolism in the development of Alzheimer's disease amyloidosis and the mechanisms by which estrogens and cholesterol-lowering drugs might exert neuroprotection. In 2005 she joined the Neuroscience and Neuropsychology of Aging Program at the National Institute on Aging where she serves as a Program Director covering research areas that address the role of metabolic and vascular factors in normal brain aging and in Alzheimer's disease. She also facilitates the development of NIA's drug discovery and preclinical drug development initiatives for AD, mild cognitive impairment and age-associated cognitive decline.

## Session IV. Issues in Technology Transfer: Interactions and Intellectual Property

*Chair – Kathleen A. Denis, PhD, Rockefeller University*

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This session will focus on the interactions among academic researchers, their technology transfer office and industry partners. An introduction will discuss the various roles and responsibilities of all of the parties involved and hope to begin to demystify academic – industry relations. The basics of patents will be presented with an emphasis on what they can and cannot successfully cover, as well as what a researcher needs to do to maximize the chances of a positive outcome. A variety of agreements used in academic – industry relationships will be discussed in the next talk, with an emphasis on the importance of creating a good relationship amongst all parties. Finally, the session will close with an honest appraisal of the good, the bad and the ugly of new company formation in the biotech industry.

### **Session Overview – Kathleen A. Denis, PhD**

#### **Working Effectively with Your TTO: Roles and Responsibilities**

Kathleen A. Denis, PhD, Rockefeller University

#### **Intellectual Property 101: A Primer For Investigators**

Colin G. Sandercock, Proskauer Rose LLP

#### **Creating Relationships with Industry: Consulting, Research, MTA's and Patent Licensing**

Louis P. Berneman, PhD, Texelerate

#### **Should You Start a Biotechnology Company?**

John S. Swartley, PhD, University of Pennsylvania



## **Kathleen A. Denis, PhD, Rockefeller University**

Kathleen A. Denis, PhD, is the Associate Vice President of Technology Transfer at The Rockefeller University, a premier biomedical research institution located in New York City. She is a Past President of the Licensing Executives Society USA/Canada (LES), and has served on the Board of Directors of the Association of University Technology Managers (AUTM) and the Pennsylvania Biotechnology Association. She is a Certified Licensing Professional.

Specializing in the management of intellectual assets in the life sciences, she has worked with academic institutions and industry clients to manage intellectual property portfolios, evaluate new technologies, market and license technologies and start new technology-based businesses. Dr. Denis is active in numerous professional organizations and speaks frequently about early stage technology evaluation, formation of start-up companies, conflict of interest and other issues of academic technology transfer.

Dr. Denis holds a Ph.D. in immunology from the University of Pennsylvania, an M.A. in Human Genetics from University of Texas Medical Branch at Galveston and an undergraduate degree in genetics from Cornell University.

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### **Working Effectively with Your TTO: Roles and Responsibilities**

Technology transfer refers to the numerous interactions between universities and industry. It can mean the publication of research, the delivery of seminars, consultancy, or the transfer of the skills and knowledge that a student brings to his or her future employers. Formally, however, the term denotes the management of intellectual property from research that is sponsored by a company but carried out at a university, and the licensing of university intellectual property to both established and start-up companies.

Technology Transfer Offices (TTO's) have been established at almost all research universities over the past 25 years. Their role is to promote and support the research enterprise at the university by creating relationships with the private sector to develop, protect, transfer and commercialize research results for the public benefit. This session will examine the legal and university policy underpinnings of technology transfer, the various tasks performed by the TTO, and how researchers can productively interact with their TTO.



## **Colin G. Sandercock, Proskauer Rose LLP**

Colin G. Sandercock is a partner in the Litigation and Dispute Resolution Department of Proskauer Rose LLP, co-chair of our Life Sciences Group, and is co-managing partner of the Washington, D.C. office. He practices in the area of life sciences, including licensing, patent and trademarks, and intellectual property. Colin was recently named in *The Best Lawyers in America* in the field of biotechnology law. Since 1984, Colin has counseled clients in life science matters including district court litigation, interferences, licensing and the management of domestic and foreign patent portfolios. His technical experience includes biotechnologies, pharmaceutical chemistry, organic and inorganic chemistry, medical devices, and chemical and biochemical engineering. Colin has served as an adjunct professor of law at George Washington University Law School, lecturing on the licensing of intellectual property rights. Colin served on the AAA Patent Advisory Committee for patent disputes, and previously chaired the Electronic Records ad hoc Subcommittee of the AIPLA Interference Committee. He also chaired the Annual Electronic Records Conferences in London in 1999, 2000, 2002 and 2004. He has served as legal counsel to CENSA (Collaborative Electronic Notebook Systems Association) and frequently lectures on the topics of electronic record keeping for use in research, litigation and interferences.

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### **Intellectual Property 101: A Primer for Investigators**

This presentation will cover basic patent law issues that researchers will encounter, including (i) the common forms of protecting IP in the biotech industry (e.g., patents, trade secrets and material transfer agreements), (ii) how to protect inventions from conception through patenting, (iii) tips for making and keeping records of invention, and (iv) inventorship and ownership. The presentation also will address some of the common pitfalls for patents involving academic researchers and practical suggestions for avoiding them.



## **Louis P. Berneman, PhD, Texelerate**

Louis P. Berneman is an experienced intellectual property licensing and business development executive. He has founded and financed intellectual property-based entrepreneurial ventures, built and managed university technology transfer programs, and has been involved in patenting and licensing since 1982 as both a licensee and licensor. Since September 2005, Lou has been the Principal of Texelerate, a consultancy specializing in monetizing intellectual property. From 1995-2005, Lou was Managing Director of the Center for Technology Transfer (CTT) at the University of Pennsylvania. Under his leadership, CTT assessed more than 3,000 technology disclosures, filed more than 1500 patents, completed more than 600 commercialization agreements including negotiating a number of substantial corporate research collaborations and creating about 80 new start up ventures, and generated more than \$100 million in license income. From 1989-1995, Berneman was Director, Licensing and Business Development at Virginia's Center for Innovative Technology patenting and licensing on behalf of the eight public research universities in Virginia. Berneman is a Past President of the Association of University Technology Managers (AUTM) and a former Vice President and Trustee of the Licensing Executives Society (LES USA & Canada). He has served as a member of the Board of the Pennsylvania Biotechnology Association, Greater Philadelphia Venture Group and the LES Foundation. Dr. Berneman is the 2005 recipient of the LES Barnes Mentoring Award, the 2003 recipient of an Award of Excellence from the Association of University Research Parks, and 2002 service award from the Pennsylvania Biotechnology Association. Berneman currently serves as an advisor and member of the Advisory Board of the Paul Capital Partners Royalty Healthcare Fund. Dr. Berneman holds a baccalaureate degree in history from the Pennsylvania State University, a teaching credential from University of California at Santa Barbara, and masters and doctoral degrees in education from Teachers College, Columbia University.

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### **Creating Relationships with Industry: MTAs, Consulting, Research, and Patent Licensing**

In recent years, an increasing number of academic institutions have created increasingly effective Technology Transfer Offices (TTOs). However, conflicting roles, values, drivers, and agendas as the bases of numerous challenges is establishing and maintaining productive relationships between academic institutions and companies. In an open innovation environment (and economy), institutions will be increasingly looked to for basic research discoveries that offer commercial potential. Despite differences and challenges, institutions and companies can collaborate to achieve mutual and respective interests.



## **John S. Swartley, PhD**, University of Pennsylvania

John S. Swartley, MBA, PhD, is Senior Director of New Ventures at the Center for Technology Transfer at the University of Pennsylvania, where he leads a team that fosters the formation of new ventures based on Penn technologies and faculty expertise. Prior to joining Penn in 2007, Dr. Swartley served as Senior Vice President and Partner of BCM Technologies (BCMT), the venture capital investment subsidiary of Baylor College of Medicine. Dr. Swartley joined BCMT in 2003 from the Yale University Office of Cooperative Research where he served as Associate Director of the Medical Campus. Dr. Swartley has participated in the formation and oversight of more than two dozen university spin-out companies that have collectively raised nearly one billion dollars of investment capital. He holds a B.S. in Biology from Bates College, an MBA from the Goizueta School of Business at Emory University, and a Ph.D. in Microbial & Molecular Genetics from Emory University.

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### **Should You Start a Biotechnology Company?**

The most recent issue of the Licensing and Activity Survey from the Association of University Technology Managers stated that 553 new start-up companies were launched from academic institutions in 2006. The same report states that over 5,700 new companies have been formed based on university technologies since 1980. These start-ups range from companies that simply take a license to university technologies, new ventures that are founded and incubated within the academic institution itself, and everything in between. Companies spun out of academia exhibit an increasingly important economic impact, locally, nationally and globally, and are one of the main drivers of numerous high tech industries, including the biotechnology industry.

This session will examine the criteria and rationale for forming new companies based on discoveries made in academia, followed by an exploration of the process of new venture formation from the scientific founders' perspective. Issues relating to founder expectations, specific roles and responsibilities, potential outcomes, and likely challenges will be covered.

## Session V. Ask the Experts: Drug Discovery for Neurodegenerative Disease

*Chair – Todd Sherer, PhD, Michael J. Fox Foundation for Parkinson’s Research*

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This breakout session will focus on disease-specific issues in drug discovery and development. The session will include 10 minute concurrent presentations from experts in Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, ALS, as well as ‘orphan’ neurodegenerative diseases. A 50-minute concurrent Q&A follows the presentations, allowing participants to ask specific questions pertaining to drug discovery. The ultimate aim of this session is to inform participants of specific issues related to the drug discovery process in certain disease areas (such as selection of animal models, target validation and pre-clinical development), to devise potential solutions to these problems and to inform the funding agencies of where cross-cutting issues should be addressed by specific funding or legislative initiatives.

### **Breakout Session Overview – Todd Sherer, PhD**

**Alzheimer’s Disease** - Frank M. Longo, MD, PhD, Stanford University

**Parkinson’s Disease** - P. Jeffrey Conn, PhD, Vanderbilt University

**Huntington’s Disease** - Leticia M. Toledo-Sherman, PhD, CHDI Foundation

**Amyotrophic Lateral Sclerosis** - Jeffrey Rothstein, MD, PhD, Johns Hopkins University

**Progressive Multiple Sclerosis** - Fred D. Lublin, MD, Mount Sinai School of Medicine



## **Todd Sherer, PhD**, Michael J. Fox Foundation for Parkinson's Research

Dr. Todd Sherer joined the Foundation as Associate Director, Research Programs, in April 2004, and was promoted to Vice President, Research Programs, in June 2006. Dr. Sherer earned his undergraduate degree in psychology from Duke University and his PhD in Neuroscience from the University of Virginia. His thesis work focused on neurotrophins and cell death pathways in neurodegenerative disease. Dr. Sherer then became a postdoctoral fellow at the Emory University laboratory of Timothy J. Greenamyre. During this fellowship, Dr. Sherer concentrated on understanding the role of environmental factors in Parkinson's disease, as well as on the development of PD model systems. As a result of this work, Dr. Sherer was awarded a Postdoctoral Fellowship from The Michael J. Fox Foundation for Parkinson's Research. Dr. Sherer is the author of over 20 research articles in the field of neurodegeneration with a focus on Parkinson's disease.



## **Frank M. Longo, MD, PhD, Stanford University**

Dr. Longo received his MD in 1981 and PhD in Neurosciences in 1983 from the University of California, San Diego. Following an internship in medicine at NYU/VA, he trained as a resident in neurology and fellow in neurobiology at University of California, San Francisco. While at UCSF he created the Neurogenetics Clinic which was the first West Coast site in the U.S. to offer DNA testing for families with Huntington's disease. He also led the creation of a national referral center for deep brain stimulation for Parkinson's disease and contributed to the development of programs in dementia, epilepsy and other areas.

At UCSF, Dr. Longo 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.

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### **Alzheimer's Disease Breakout**

A number of fundamental issues continue to challenge drug development efforts in AD. Variants of the amyloid hypothesis continue to dominate current perspectives on etiological mechanisms; however, the likelihood that mechanisms in addition to amyloid accumulation contribute to disease progression renders target validation an ongoing critical issue. It remains quite possible that no single targeting strategy will be capable of slowing the underlying, robust and multifactorial biology of AD, but instead, multiple processes will have to be modulated in a substantial way. Perhaps further development of large scale 'omic' approaches (i.e. the receptosome etc) will aid in prioritizing candidate targets. The spectrum of animal models has expanded; however, in most cases multiple genetic perturbations are required to generate a degree of pathology at least somewhat resembling that seen in the human disorder. The extent to which these combination transgenic models are relevant to so called sporadic AD remains unknown. Another limitation in the preclinical AD field is that endpoints have been largely limited to lowering amyloid beta levels and/or plaque load and water maze testing. Treatments are tested at relatively early stages well before neuronal loss occurs. A number of strategies might be employed in order to improve the predictive value of animal models. These might include testing at more advanced stages of pathology during which age-related factors might play a greater role, applying multiple morphological and behavioral endpoints and developing higher order mammalian models. Each of these alternatives would be difficult under current academic and grant funding models. Another key hurdle in pre-clinical development is that a major portion of target discovery and initial validation is conducted in academic labs outside of a setting in which target tractability and other drug development expertise is readily available.



## P. Jeffrey Conn, PhD, Vanderbilt University

Dr. Conn is the Lee E. Limbird Professor of Pharmacology at Vanderbilt University and Director of the Vanderbilt Program in Drug Discovery. Dr. Conn received the PhD degree in Pharmacology from Vanderbilt University in 1986 and pursued postdoctoral studies in the Department of Pharmacology at Yale University. Dr. Conn joined the faculty of the Department of Pharmacology at Emory University in 1988 where he rose to the rank of Full Professor and established himself as a leader in studies of neurotransmitter receptors and their roles in regulating brain function in circuits involved in psychiatric and neurological disorders. In 2000, Dr. Conn moved to Merck and Company to assume the position of Senior Director and Head of the Department of Neuroscience at Merck's site in West Point, PA. Dr. Conn moved to Vanderbilt University in 2003 to start a new Program in Drug Discovery, with a primary mission of facilitating translation of recent advances in basic science to novel therapeutics. Dr. Conn is Editor in Chief of *Molecular Pharmacology*, Regional Editor (North America) of *Current Neuropharmacology* and serves on the editorial boards of 6 other international journals. Dr. Conn serves on the Scientific Advisory Boards of Addex Pharmaceuticals, Precient Neuropharma, Invitrogen Life Technologies, Seaside Therapeutics, Cephalon Inc., AstraZeneca US, Hoffman La Roche, Michael J. Fox Foundation, and the Dystonia Medical Research Foundation and Eyeforpharma Advisory Board on CNS Drugs. He is Chairman of the Neuropharmacology Division of the American Society for Pharmacology and Experimental Therapeutics (ASPET). He serves on several national and international committees, including International Union of Pharmacology (IUPHAR) subcommittee on receptor nomenclature, the American Society for Pharmacology and Therapeutics (ASPET) Publications Board of Trust, ASPET Awards Committee, and is an Expert Consultant, Compound Selection Committee, Treatment Units for Research on Neurocognition and Schizophrenia (TURNS). Dr. Conn's current research is focused on development of novel treatment strategies for schizophrenia, Parkinson's disease, and other brain disorders.

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### Allosteric Potentiators of mGluR4 as a Novel Approach to Treatment of Parkinson's Disease

Anatomical, cellular, molecular, and behavioral studies suggest that agonists of the metabotropic glutamate receptor mGluR4 could provide a novel approach to treatment of Parkinson's disease by actions at a key synapse in the basal ganglia motor circuit. mGluR4 is highly localized at the striato-pallidal synapse, a synapse that is thought to be overactive in Parkinson's patients. Agonists of mGluR4 reduce transmission at this synapse and have robust antiparkinsonian effects in animal models. Unfortunately, it has been difficult to develop highly selective agonists of mGluR4 that have suitable properties for use as drugs. The glutamate binding site is highly conserved across mGluR subtypes, making it difficult to develop highly selective ligands. Also, glutamate site agonists are analogs of glutamate and do not possess pharmacokinetic properties needed to allow them to be useful as drugs. In addition, there are a number of problems associated with the use of agonists as drugs, including adverse effects of excessive receptor activation, profound receptor desensitization, and loss of activity dependence of receptor activation. We have discovered a broad range of structurally diverse novel allosteric potentiators of mGluR4. These compounds have no effect on mGluR4 when added alone but induce progressive leftward shifts in the agonist concentration-response curve for activation of this receptor. In addition, these compounds potentiate mGluR4-mediated inhibition of transmission at the striato-pallidal synapse, a synapse that is thought to be critical for antiparkinsonian effects of mGluR4 receptor agonists. Furthermore, these compounds induce behavioral effects in rodent models of Parkinson's disease. These findings provide an exciting advance and support view that allosteric potentiators of may provide a viable novel approach to developing agents that regulate mGluR4 and other GPCRs. *Supported by NIH and the Michael J. Fox Foundation for Parkinson's Research.*

## **Leticia M. Toledo-Sherman, PhD, CHDI Foundation**

Leticia Toledo-Sherman directs drug discovery projects at CHDI combining her expertise in the areas of medicinal and computational chemistry. Before joining CHDI in 2005, she was Executive Director of Chemistry at LymphoSign Inc., where she managed medicinal and computational chemistry as well as associated research relationships. Prior to LymphoSign Inc, Toledo-Sherman directed drug design and discovery activities at Protana Inc. (formerly MDS Proteomics). There, she led several successful discovery and lead optimization projects and managed the company's Chemical Proteomics program. The latter involved a multidisciplinary team working at multiple sites. Before Protana, Toledo-Sherman worked at Kinetix Pharmaceuticals Inc. (acquired by Amgen in December 2000), one of the earliest successful biotech companies to focus exclusively on targeted kinase inhibition. While at Kinetix, she designed and implemented a Computer-Aided Design and Virtual Screening platform that led to the discovery of several novel potent small molecule inhibitors of protein kinases. Toledo-Sherman holds a PhD in Organic Chemistry from SUNY Stony Brook. She did postdoctoral research at MIT and the Skaggs Institute of Chemical Biology at The Scripps Research Institute.

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### **Design and Optimization of Kynurenine Monooxygenase Inhibitors as Therapeutic Agents for Huntington's Disease**

Inhibitors of Kynurenine monooxygenase KMO, an enzyme in the Kynurenine pathway of tryptophan metabolism, may hold potential as neuroprotective agents for neurodegenerative diseases in particular Huntington's disease as several metabolites in the pathway may have neurodegenerative activities. Furthermore, 3-hydroxy kynurenine, the direct product of KMO has also been shown to be a neurotoxic agent and involved in the development of reactive oxygen species (ROS) that lead to oxidative stress and cell death. CHDI has undertaken the design and optimization of several classes of potent and selective KMO inhibitors using an integrated program comprising medicinal chemistry, computational chemistry, biology and the use of routine ADME determinations. Using this integrated target-based approach, the group has been able to design compounds with good brain-blood barrier permeability that should serve as proof-of-concept compounds for in vivo efficacy studies in HD and potentially as therapeutics with utility in the clinic.



## **Jeffrey Rothstein, MD, PhD, Johns Hopkins University**

Dr. Rothstein is Professor of Neurology and Neuroscience and a faculty member of the Graduate Program in Cellular and Molecular Medicine at Johns Hopkins University. He is the Director of the Robert Packard Center for ALS Research at Johns Hopkins, the Co-Director of the Brain Science Institute (BSI) and the Director of the BSI Neurotranslation Program. He directs the MDA/ALS Clinic and oversees one of the largest ALS clinics in the USA.

In 2000 Dr. Rothstein organized the Robert Packard Center for ALS Research at Johns Hopkins and serves as medical Director. This is the first multi-Institutional, Multi-National collaborative academic organization devoted toward understanding the cause of ALS and translating the information into new drug and cell based therapies. It uses an aggressive model of funding research among the leading young and senior researchers with funding based on performance expectations and mandatory collaboration. Currently the Center funds approximately 30 researchers, spending \$2-3 million/yr. In the last 5 years the vast majority of leading ALS achievements, by researchers from around the country, has been the result of the various investigators supported via this approach. In recent years the collaboration has been extended to ALS and Neurodegenerative Disease non-profit organizations and NIH. The approach has led to the unprecedented generation of new animal models of the disease and new clinical therapeutic targets.

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### **Synaptic Dysregulation of Astroglial Function in Neurodegeneration: Target for Drug Therapy**

Astrocytes play an essential role in the regulation of synaptic glutamate. The communication for this regulation between neuron/axon and astroglia remains unknown. In disease settings, severe disruption of this neuron-glia network, as reflected by a loss of synaptic astroglial glutamate transporter EAAT2/GLT1 and the metabolic transporter MCT1, has been repeatedly documented. Disruption of this astroglial function is a potentially toxic mechanism that acts to promote disease progression in neurodegeneration associated with Amyotrophic Lateral Sclerosis (ALS). We will show that synaptic inputs from neuron to astroglia are essential and sufficient for astroglial transporter expression. We have now identified the molecular pathway that regulates astroglial responses to synaptic input. Synaptic terminals regulate astroglial GLT1/EAAT via kappa B-motif binding phosphoprotein (KBBP), the mouse homologue of human heterogeneous nuclear ribonucleoprotein K (hnRNP K), which binds to an essential element of EAAT2/GLT1 promoter. This neuron-stimulated factor is required for EAAT2/GLT1 transcriptional activation and is responsible for astroglial alterations in neural injury. Denervation of neuron-astrocyte signaling *in vivo*, by acute corticospinal tract transection or ricin-induced motor neuron death, as well as chronic neurodegeneration in a rodent model of amyotrophic lateral sclerosis results in reduced astroglial KBBP expression and transcriptional dysregulation of astroglial transporter expression. Our studies indicate that synaptic elements dynamically coordinate normal astroglial function and also provide a fundamental signaling mechanism by which altered neuronal function and injury leads to dysregulated astroglia in CNS disease. Our studies also indicate that a more complete understanding of the global transcriptional changes in astrocytes following neuronal injury may help identify other pathways by which astroglia contribute to normal and abnormal brain function. We have used this information to design a series of drug discovery systems that target astroglial dysfunction, repair of astroglia and generation of new astroglia.



**Fred D. Lublin, MD, Mount Sinai School of Medicine**

Fred D. Lublin, M.D. is the Saunders Family Professor of Neurology at Mount Sinai School of Medicine and Director of the Corinne Goldsmith Dickinson Center for Multiple Sclerosis at that institution. Dr. Lublin received his medical degree in 1972 from Jefferson Medical College, Philadelphia, PA. He completed his internship in Internal Medicine from the Bronx Municipal Hospital, Albert Einstein Medical Center, and his residency at the New York Hospital, Cornell Medical Center.

As a neuroimmunologist, Dr. Lublin has a special interest in immune functions and abnormalities affecting the nervous system. He has been involved in both basic science and clinical research. He and his colleagues were among the first in the country involved with studies of Interferon beta-1b, which was approved by the Food & Drug Administration in 1993 to treat the relapsing-remitting form of Multiple Sclerosis. He is currently involved with several new clinical research protocols on promising agents for treating various aspects of MS. He was chairman of the National MS Society (USA) advisory committee on clinical trials of new drugs in Multiple Sclerosis and the National Multiple Sclerosis Society's Research Programs Advisory Committee. He is a member of the National MS Society National Board of Directors and their medical advisory board. Dr. Lublin and his colleagues at the National MS Society have re-defined the clinical course definitions of MS using data from a survey of the international MS community. He has chaired a task force on the ethics of placebo-controlled trials in MS. Dr. Lublin was a member of the panel that redefined the diagnostic criteria for MS. Dr. Lublin has published numerous scientific articles and belongs to many professional societies and advisory boards. Dr. Lublin has served as a consultant to the National Institutes of Health and to many pharmaceutical/biotech companies in all phases of new drug development and in preparation for presentation to the FDA and their advisory panels. He is the Principal Investigator of the NIH-sponsored multicenter Combination Therapy study in Multiple Sclerosis.

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**Progressive Multiple Sclerosis**

While there are effective therapies for the relapsing forms of MS, treatment of progressive MS has lagged behind; this includes primary progressive MS, secondary progressive MS and progressive relapsing MS. The current therapeutic approach centers around anti-inflammatory agents, which do not seem to provide as much efficacy in progressive disease as they do for early, relapsing MS. This may be due to shifts in the underlying pathophysiology from an inflammatory based pathology to a neurodegenerative process. Differences in trial design and outcome measures may also play a role. Plans have been underway for developing effective trial designs for progressive disease and on how to best employ a neuroprotective strategy. Utilization of advanced MRI metrics will be utilized along with the clinical outcome measures. Such an approach would nicely complement current therapies and provide potential benefit to a very large number of individuals with MS.

## Session VI. Resources and Services for Advancing Drug Discovery

*Chair — Lorenzo Refolo, PhD, National Institutes of Health/ National Institute of Neurological Disorders and Stroke*

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This session will focus on descriptions of the resources available through a variety of mechanisms within academia, the National Institutes of Health (NIH), foundations and commercial vendors. Speakers will focus on resources for assay development, target identification, drug discovery, drug development, pre-clinical toxicology evaluation and other components needed for the translation of pre-clinical drug candidates into potential therapies tested in clinical trials. In particular, it will include specific descriptions of programs available to academic investigators through individual NIH Institutes, including the National Institute on Aging (NIA) and the National Institute of Neurological Disorders and Stroke (NINDS), as well as trans-NIH programs including the NIH *Roadmap for Medical Research* and the NIH *Blueprint for Neuroscience Research*.

### **Session Overview – Lorenzo Refolo, PhD**

#### **ADDME - Avoiding Drug Development Mistakes Early**

Katya Tsaïoun, PhD, Apredica

#### **Resources at the National Institute of Health**

Suzana Petanceska, PhD, National Institutes of Health/National Institute on Aging and  
Lorenzo Refolo, PhD, National Institutes of Health/National Institute of Neurological  
Disorders and Stroke

#### **Academic Models of Drug Discovery Services**

D. Martin Watterson, PhD, Northwestern University



## **Katya Tsaion, PhD, Apredica**

Dr. Tsaion earned her M.S. degree in solid-state chemistry from the Leningrad Institute of Technology, and her Ph.D. from Tufts University. Her Ph.D. thesis on the effects of signal transduction and apoptosis factors in the rat brain was done under direction of Drs. James Sadowski and James Joseph in the Neuroscience Laboratory. She completed her academic training in the Neurochemistry Department at the Harvard University Primate Center, working on *in vivo* and *in vitro* drug-dependence models with cannabinoid receptor and dopamine transporter systems. Prior to founding Apredica, Dr. Tsaion worked as a Group Leader at Surface Logix, where she built a team and developed a complete *in vitro* ADME and *in vivo* DMPK (drug metabolism and pharmacokinetics) program, which were a central part of the company's technology platform for optimizing and advancing drug leads in CNS and oncology therapeutic areas. Prior to Surface Logix, Dr. Tsaion worked at Mitotix (subsequently merged into GPC Biotech), where she pioneered cell-based assay development in the area of angiogenesis (oncology) and infectious disease. While at GPC Biotech, Dr. Tsaion managed the outsourcing of a battery of *in vitro* ADME assays and introduced and pioneered the establishment of in-house *in vitro* ADME capabilities, developing and validating a high-to-medium-throughput ADME assay panel and bringing in house *in silico* ADME prediction models. Apredica specializes in rapid preclinical *in vitro* assessment of the ADME Tox (Absorption, Distribution, Metabolism, Elimination and Toxicity) properties of small-molecule and peptide therapeutics.

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### **ADDME - Avoiding Drug Development Mistakes Early**

The talk will focus on the impact of *in vitro* ADMET studies and how they can be used in lead optimization and preclinical development programs. Case studies of using early ADME studies designed using FDA Guidance documents will be presented.

The FDA has released two guidance documents stressing the importance of understanding of drug transport and metabolism for the submission of an Investigational New Drug (IND). The FDA guidance document of September 2006 for *in vitro* drug-drug interaction studies outlined a logical approach for drug-drug interaction and transport studies. These studies, when implemented following a flowchart suggested by the FDA, allow pharmaceutical companies to save resources and move faster through both the preclinical and clinical phases of drug development. This flowchart will be presented, along with strategies for following the FDA's outline, illustrated by case studies.

In February 2008 the FDA released a new guidance document regarding the safety evaluation of metabolites (Guidance for Industry, Safety Testing of Drug Metabolites, FDA, February 2008). The FDA is now requiring that before any New Chemical Entity (NCE) can be approved for clinical research, the NCE's metabolites must be identified and subjected to preclinical toxicity testing to ensure safety.

Heretofore, the study of metabolites has been pushed into late development due to the high cost and long timelines required for *de novo* synthesis of metabolites. This new FDA guidance is now making early access to metabolites increasingly important, as access in the discovery phase enables faster and better determinations of whether a drug candidate merits further development.

Current methods commonly used for metabolite production, however, are ill suited for the financial and time constraints of the drug discovery process. Yet, early identification of metabolic or toxicity issues would result in substantial financial and time savings as metabolites, like drug candidates, can be toxic or pharmacologically active. The earlier the metabolite properties are known, the fewer resources are wasted on drug candidates that have no future. Case studies of where early knowledge of metabolism impacted the fate of programs will be presented.



**Lorenzo M. Refolo, PhD**, National Institutes of Health/National Institute of Neurological Disorders and Stroke

Dr. Lorenzo M. Refolo received a BSc. from the University of Connecticut, and was awarded a Ph.D. in Molecular Genetics from the Department of Molecular Genetics at the Rutgers University School of Medicine and Dentistry. Subsequently, Dr. Refolo trained as a post-doctoral fellow at Mt Sinai Medical Center in New York, investigating the molecular and cell biology of the Alzheimer's Amyloid Precursor Protein. After concluding his post-doctoral training Dr. Refolo served as Transgenics Group Leader at Athena Neurosciences and later held faculty positions at the Mayo Clinic Jacksonville and New York University's Nathan Kline Institute for Psychiatric Research. In 2001, Dr. Refolo was named the Scientific Director at the Institute for the Study of Aging, a private, disease-focused foundation with a mission to fund the discovery and clinical development of drugs for the treatment of Alzheimer's disease. Since 2005, Dr. Refolo is Program Director in the Neurodegeneration Cluster at NINDS where his major responsibility is the management of a portfolio of grants on ALS, Alzheimer's and Parkinson's diseases and Vascular Cognitive Impairment.

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## **Translational Research Initiatives for Neurodegeneration at the NIH**

This presentation will be an overview of trans-NIH resources and programs available to academic investigators involved in drug discovery. We will also outline the translational research initiatives that NIA and NINDS have in place to support drug discovery and preclinical drug development for Alzheimer's disease and other major neurodegenerative disorders.



## **D. Martin Watterson, PhD, Northwestern University**

Dr. Watterson is Co-Director of the University Center for Drug Discovery and Chemical Biology and holds the John G. Searle Endowed Chair in Molecular Biology and Biochemistry at Northwestern University. He also 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. His Ph.D. training was in the areas of Biophysical Chemistry and Biochemical Pharmacology at Emory University, followed by postdoctoral training at Duke University Medical Center supported by a National Research Service Award in Neurosciences from the National Institutes of Health 1975 to 1977. 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 in 1994. In his role as Co-Director of the Center for Drug Discovery and Chemical Biology, Dr. Watterson has facilitated the development of novel compounds emanating from Center investigators and their movement towards the clinic. Center investigators experiences span the range of the entire drug discovery and development spectrum, including novel compound discovery, candidate compound optimization, preclinical IND-enabling studies, clinical trials, and FDA approval.

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### **Academic Models of Drug Discovery Services**

This presentation will summarize selected examples of support models in academia for drug discovery research. These models range from those based on highly skilled technology platforms to broader intellectual infrastructure support including consultation and support of project initiation. Issues to be addressed will include the key steps in preclinical drug discovery that are often barriers in academia, as well as the importance of the support to local academic missions and the critical needs of investigator-initiator research. The organizational structures range from complete service and cost-recovery operations for the key steps in preclinical discovery research to facilitation of academia-industry-government cooperative efforts.

# Foundation Resources Panel

*Chair: Howard Fillit, MD, ADF*

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*Panelists:*

Lucie Bruijn, PhD, ALS Association

Antony Horton, PhD, International Rett Syndrome Foundation

Cynthia Joyce, SMA Foundation

Todd Sherer, PhD, Michael J. Fox Foundation for Parkinson's Research

Leticia Toledo-Sherman, PhD, CHDI Foundation



**Lucie Bruijn, PhD**, ALS Association—Lucie Bruijn, PhD joined The ALS Association in January 2001 as Science Director and Vice President. Prior to that Dr. Bruijn led a team at Bristol Myers Squibb developing in vitro and in vivo model systems for neurodegenerative disease. She focused on developing an improved mouse model for Alzheimer’s disease and established assays for high throughput screens. She worked with the Genomics group and used array technology to look for new therapeutic targets. Realizing the potential of stem cell therapy for neurodegenerative diseases, her team worked with experts in academia to establish stem cell studies. Dr. Bruijn received her Bachelor’s degree in Pharmacy at Rhodes University, South Africa. She received a Master’s degree in Neuroscience and a PhD in Biochemistry, specializing in disease mechanisms of Alzheimer’s disease, at the University of London, United Kingdom. She joined Dr. Don Cleveland’s laboratory at Johns Hopkins University in 1994 where she developed and characterized a mouse model of ALS (mice expressing the familial-linked SOD1 mutation). Using this model her studies focused on disease mechanisms. In addition, in collaboration with Dr. Robert Brown she looked for neurofilament mutations in familial and sporadic ALS patients. At The ALS Association, Dr. Bruijn leads ALS research effort. She has expanded on the existing grant programs, launching a new research initiative Translational Research to Advance Therapies for ALS (TREAT ALS) with the goal to move treatment options from “bench to bedside.”



**Antony Horton, PhD**, International Rett Syndrome Foundation—Dr. Horton is Chief Scientific Officer of the International Rett Syndrome Foundation, the world’s leading private funder of basic and clinical Rett syndrome research. Prior to this, Dr. Horton served as the Director of Scientific Affairs of the Alzheimer’s Drug Discovery Foundation. He gained his Doctoral degree at St. Andrews University in Scotland U.K., where he was trained in the areas of developmental neurobiology and neuronal cell survival. Following this, he conducted four years of post-doctoral research into neurodegenerative diseases at the Rockefeller University in New York. Dr. Horton has published on aspects of neurodegeneration and neuronal cell survival in a number of research papers and journal articles. Dr. Horton had 5 years experience working in a non-profit setting, where as Program Director at the Juvenile Diabetes Research Foundation, he led a small team that helped set the research agenda for Diabetes Complications.



**Cynthia Joyce**, SMA Foundation—Cynthia Joyce has worked with the SMA Foundation since its inception to build momentum in research and therapeutics development for spinal muscular atrophy. Over the last five years, the Foundation has facilitated a five-fold increase in research dollars allocated by federal, corporate and non-profit funders and has itself emerged as the leading single sponsor of research in the field. A member of the Executive Committee, Ms. Joyce works closely with the leadership to establish and execute strategies addressing the Foundations research goals and mission. As Executive Director, she is responsible for the day-to-day operations of the Foundation, including grant making, corporate and pharmaceutical/biotech business development and public relations. Ms. Joyce is also serving as Acting Director for Clinical Research. Prior to joining the Foundation, Ms. Joyce served as Director of the American Academy of Neurology (AAN) Foundation and as marketing director at Cephalon and at Ciba Pharmaceuticals (now Novartis). She holds a Bachelor of Science degree from the University of Chicago and an MS in Botany from the University of Minnesota. She has served as an advisor to numerous organizations including NINDS, the Epilepsy Foundation, the ALS Association and many others. She is currently serving on the Board of Directors of ASENT, the American Society for the Experimental Neurotherapeutics.

# The 10<sup>th</sup> International Conference on **ALZHEIMER'S DRUG DISCOVERY**

September 2009 • *New York, NY*

*Presented by the Alzheimer's Drug Discovery Foundation*

The conference will bring together academic and industry scientists to accelerate the development of novel drug discovery programs for Alzheimer's disease. It will offer updates on ongoing research, as well as highlight new studies and concepts.

This ADDF meeting is the only conference that focuses on the development of innovative drugs targeting Alzheimer's disease and related dementias.

## **Conference objectives:**

- To discuss scientific progress on drug discovery programs aimed at treating Alzheimer's disease and related dementias.
- To increase networking opportunities for scientists to share information and resources.



**[www.alzdiscovery.org](http://www.alzdiscovery.org)**