

8th ANNUAL DRUG DISCOVERY FOR NEURODEGENERATION CONFERENCE:

An Intensive Course on Translating Research into Drugs

February 2-4, 2014 • Miami, Florida

Presented by the Alzheimer's Drug Discovery Foundation



www.alzdiscovery.org

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LIST OF ABBREVIATIONS

- **ADMET** (absorption, distribution, metabolism, excretion)
 - Absorption-ability of drug to penetrate the GI tract to the circulatory system
 - Distribution-solubility of drug in blood, binding to plasma proteins
 - Metabolism -chemical modifications of drug (e.g. by cytochrome P), amount available to reach target
 - Excretion-mechanisms of drug elimination from the body
 - Toxicity
- **API**-Active pharmaceutical ingredient
- **BBB**-Blood brain barrier
- **CMC**-Chemistry, manufacturing, control
- **CNS**-Central nervous system
- **CRO**-Contract research organization
- **CSF**-Cerebral spinal fluid
- **CYP450**-Cytochrome P450 enzyme family
- **FDA**-Food and Drug Administration
- **EMA**-European Medicines Agency
- **FBLD**-Fragment based lead discovery
- **FTE**-Full time employee
- **GCP**-Good clinical practice
- **GLP**-Good laboratory practice
- **GMP**-Good manufacturing practices (cGMP)
- **HCS**-High content screening
- **hERG**-Human ether-a-go-go gene
- **HTS**-High throughput screening
- **IND**-Investigational new drug
- **IRB**-Institutional review board
- **LC-MS/MS**-Liquid chromatography coupled with tandem mass spectrometry
- **LOEL**-Lowest observed effect level
- **logP-Octanol**-water partition coefficient
- **MW**-Molecular weight
- **NCE**-New chemical entity
- **NDA**-New drug application
- **NIA**-National Institute of Aging
- **NIH**-National Institute of Health
- **NINDS**-National Institute of Neurological Diseases and Stroke
- **NOAEL**-No observable adverse effect level
- **NOEL**-No observable effect level
- **MTD**-Maximum tolerated or minimally toxic dose
- **PD**-Pharmacodynamics
- **PK**-Pharmacokinetics
- **POC**-Proof of concept
- **PSA**-Polar surface area
- **QSAR**-Quantitative structure activity relationship
- **SAR**-Structure-activity relationship
- **SBIR**-Small Business Innovation Research Award
- **SOP**-Standard operating procedure
- **STTR**-Small Business Technology Transfer
- **TI**-Therapeutic index, ratio between the dose that produces toxic effects to the dose needed for therapeutic response.
- **Toxicokinetic parameters:**
 - **AUC** = area under the plasma concentration vs. time curve
 - **C_{max}** = maximum plasma concentration
 - **T_{max}** = time to achieve maximum plasma concentration
 - **T_{1/2}** = elimination half-life
 - **F** = percent bioavailability
- **TPP**-Target product profile

ABOUT THE ALZHEIMER'S DRUG DISCOVERY FOUNDATION



Alzheimer's
Drug Discovery
Foundation

CONQUERING ALZHEIMER'S THROUGH DRUG DISCOVERY

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

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

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

WHAT WE'VE ACCOMPLISHED

1. The ADDF has granted more than **\$65 million to fund nearly 450 Alzheimer's drug discovery programs and clinical trials** in academic centers and biotechnology companies in **18 countries**.
2. As a measure of success, programs funded by the ADDF have gone on to receive commitments of nearly **\$3 billion** in follow-on funding from the government, pharmaceutical companies and venture capital firms.
3. In 2012, the Alzheimer's Drug Discovery Foundation (ADDF) launched the ADDF ACCESS program to give the academic and small biotechnology community online access to a marketplace of contract research organizations (CROs) and a virtual network of expert consultants and collaborators who focus on drug discovery for diseases of the central nervous system (CNS). ADDF ACCESS additionally provides educational resources and guidance on the process of selecting and managing a CRO contract¹. Register for free at www.alzdiscovery.org/research-and-grants/addf-access/.

¹ Lane RF, Friedman LG, Keith C, Braithwaite SP, Frearson JA, Lowe DA, Longo FM, Refolo L, Watterson DM, Tsaion K, Shineman DW, Fillit HM (2013). Optimizing the use of CROs by academia and small companies. Nature Reviews Drug Discovery Vol.12; 487-488

ADDF ANNUAL CONFERENCES

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

SCIENTIFIC ADVISORY COMMITTEE

Kurt Brunden, PhD, University of Pennsylvania

Howard Fillit, MD, Alzheimer's Drug Discovery Foundation

Marcie Glicksman, PhD, Harvard Medical School

Rachel Lane, PhD, Alzheimer's Drug Discovery Foundation

Frank Longo, MD, PhD, Stanford University

Kalpana Merchant, PhD, Eli Lilly and Company

Suzana Petanceska, PhD, National Institute on Aging

Diana Shineman, PhD, Alzheimer's Drug Discovery Foundation

Edward Spack, PhD, Fast Forward LLC

D. Martin Watterson, PhD, Northwestern University

CONFERENCE DELIVERABLES

A webcast of the entire conference will be made available on the Alzheimer's Drug Discovery Foundation website (www.alzdiscovery.org), where you may also access a webcast of last year's conference.

WELCOME NOTES



On behalf of the **Alzheimer's Drug Discovery Foundation (ADDF)**, I am pleased to welcome you to the 8th *Drug Discovery for Neurodegeneration Conference: An Intensive Course on Translating Research into Drugs*.

Designed as a comprehensive course on the drug discovery process, from target validation through to clinical development, this annual *Drug Discovery for Neurodegeneration* conference provides participants with the fundamental knowledge and resources to translate their research into new drugs to treat and prevent Alzheimer's disease and related neurodegenerative diseases.

I would like to personally thank our scientific advisory committee, session chairs and speakers for their dedication and commitment to this meeting. Your expertise in the field and willingness to share lessons learned has helped to make this course possible.

We encourage you to visit the poster presentations by our talented Young Investigator Award and Scholarship winners. We are proud of their efforts and encourage them to continue pursuing their work in the neurodegeneration field.

This year, we are pleased to host the meeting in Miami, Florida, which boasts over 100 biotechnology companies, 90 pharmaceutical & biopharmaceutical companies, and 400 medical device manufacturing companies. It is a top 5 state for bioscience employment, and bioscience job growth in Florida is 5% greater than the national average. We are thrilled to be able to participate in this community and bring our conference to this progressive state.

Our meeting is made possible by the generous support of partners and sponsors: the National Institute on Aging, Merck & Co., Inc., The Michael J. Fox Foundation for Parkinson's Research, National Multiple Sclerosis Society, Biogen Idec, Cyprotex and Brains On-Line. We would also like to thank our media partners for their commitment to making this meeting a success.

We are proud to welcome attendees from all over the world and are looking forward to a stimulating and educational two and half days. Thank you for joining us!

Howard

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

8th ANNUAL DRUG DISCOVERY FOR NEURODEGENERATION CONFERENCE: AN INTENSIVE COURSE ON TRANSLATING RESEARCH INTO DRUGS PROGRAM

Sunday, February 2, 2014

2:00 – 4:00	Registration
4:00 – 4:20	Welcome & Opening Remarks: Challenges and Opportunities in Academic Drug Discovery Howard Fillit, MD, <i>Alzheimer's Drug Discovery Foundation</i>
4:20 – 5:05	Plenary: Functional Approaches to CNS Drug Discovery and the Potential for Drugs with Multiple Targets as a Mechanism of Action Frank Sams-Dodd, PhD, DSc, <i>Willingsford Ltd</i>
5:05 – 5:15	Q&A
5:15 – 5:20	Closing Remarks Howard Fillit, MD, <i>Alzheimer's Drug Discovery Foundation</i>
5:20 – 7:00	Welcome Reception

Monday, February 3, 2014

8:00 – 8:30	Continental Breakfast & Registration	
8:30 – 8:35	Welcome and Opening Remarks Lorenzo Refolo, PhD, <i>National Institute on Aging</i>	
8:35 – 8:50	Preclinical Therapeutics Development for Neurological Disorders: Funding and Resources Lorenzo Refolo, PhD, <i>National Institute on Aging</i> and Patricia Ann Walicke, MD, PhD, <i>National Institute of Neurological Disorders and Stroke</i>	
I. Introduction to Small Molecule Chemistry for Biologists Chair: D. Martin Watterson, PhD, Northwestern University		
8:50 – 9:25	Overview: Themes in Successful Prior Art for Novel Small Molecule Discovery in CNS Disorders D. Martin Watterson, PhD, <i>Northwestern University</i>	
9:25 – 9:35	Q&A	
9:35 – 10:10	Synthetic Chemistry Fundamentals in Lead Compound Refinement Jeff Pelletier, PhD, <i>Fox Chase Chemical Diversity Center, Inc.</i>	
10:10 – 10:20	Q&A	
10:20 – 10:40	Natural Products as Drug Starting Points Frank Koehn, PhD, <i>Pfizer Inc.</i>	
10:40 – 10:50	Q&A	
10:50 – 11:20	Break	
II. Embarking on a Drug Discovery Campaign Chair: Kalpana Merchant, PhD, Eli Lilly and Company		
11:20 – 11:25	Session Overview Kalpana Merchant, PhD, <i>Eli Lilly and Company</i>	
11:25 – 11:45	De-risking Parkinson's Disease Drug Development via Optimal Target Validation and Decision-driving Biomarkers Kalpana Merchant, PhD, <i>Eli Lilly and Company</i>	
11:45 – 11:55	Q&A	
11:55 – 12:15	Using Chemical Probes for Target Validation and to Understand Target Liability Jian Jin, PhD, <i>University of North Carolina at Chapel Hill</i>	
12:15 – 12:25	Q&A	
12:25 – 12:45	Assembling the Right Interdisciplinary Team From the Beginning Julie Frearson, PhD, <i>Biofocus</i>	
12:45 – 12:55	Q&A	
12:55 – 1:55	Lunch and Poster Session	BREAKOUT I. Emerging Trends and Practical Aspects of Medicinal Chemistry Refinement
III. Drug Discovery: From Screening to Clinical Candidate Chair: Edward Spack, PhD, Fast Forward, LLC		
1:55 – 2:00	Session Overview Edward Spack, PhD, <i>Fast Forward, LLC</i>	
2:00 – 2:20	New Trends in High Throughput Screening (HTS): Rapid and Inexpensive Discovery of Natural Product-like Molecules for Probe and Drug Development Thomas Kodadek, PhD, <i>Scripps Florida</i>	
2:20 – 2:30	Q&A	
2:30 – 2:50	Compound Optimization after HTS: From Hit to Lead Kurt Brunden, PhD, <i>University of Pennsylvania</i>	
2:50 – 3:00	Q&A	
3:00 – 3:20	Designing a Therapeutic Animal Study: Employing Translatable Biomarkers Manfred Windisch, PhD, <i>NeuroScios - Neuroscience Optimized Solutions</i>	
3:20 – 3:30	Q&A	
3:30 – 3:50	Break	

3:50 – 4:10	Requirements for an IND and Early Considerations Edward Spack, PhD, <i>Fast Forward, LLC</i>
4:10 – 4:20	Q&A
4:20 – 4:40	When Should You Engage a Contract Research Organization? Katya Tsaïoun, PhD, <i>Pharma Launcher</i>
4:40 – 4:50	Q&A
4:50 – 5:10	ADDF ACCESS Program and Closing Remarks Rachel Lane, PhD, <i>Alzheimer's Drug Discovery Foundation</i>
5:10 – 5:30	Break: Networking Tips Session-University of Miami Toppel Career Center
5:30 – 6:30	Networking Reception and Poster Session

Tuesday, February 4, 2014

8:00 – 8:30	Continental Breakfast	
8:30– 8:35	Welcome & Opening Remarks Diana Shineman, PhD, <i>Alzheimer's Drug Discovery Foundation</i>	
8:35– 9:05	Plenary: The Story of Lyrica: Academic Discovery to Commercial Success Richard Silverman, PhD, <i>Northwestern University</i>	
9:05 – 9:15	Q&A	
IV. Strategies for Challenging CNS Targets – Case Study Examples Chair: Marcie Glicksman, PhD, Harvard NeuroDiscovery Center		
9:15 – 9:20	Session Overview Marcie Glicksman, PhD, <i>Harvard NeuroDiscovery Center</i>	
9:20 – 9:40	Case Study: From Bench to High Throughput Screen Marcie Glicksman, PhD, <i>Harvard NeuroDiscovery Center</i>	
9:40 – 9:50	Q&A	
9:50 – 10:10	Innate Immune Modulatory Strategies for ALS and Alzheimer's Todd Golde, MD, PhD, <i>University of Florida</i>	
10:10 – 10:20	Q&A	
10:20 – 10:40	Development of Small Molecule Hepatocyte Growth Factor Mimetic for the Treatment of Dementia Joseph Harding, PhD, <i>M3 Biotechnology</i>	
10:40 – 10:50	Q&A	
10:50 – 11:10	Break	
11:10 – 11:30	Allopregnanolone: From Laboratory Discovery to Clinical Trial Robert Diaz Brinton, PhD, <i>University of Southern California</i>	
11:30 – 11:40	Q&A	
11:40 – 12:00	BACE Inhibition for Alzheimer's Disease: Validation of Target Engagement Mark Forman, MD, PhD, <i>Merck & Co., Inc.</i>	
12:00 – 12:10	Q&A	
12:10 – 1:10	Lunch and Poster Session	BREAKOUT II. Discussion on Lessons Learned with Case Study Speakers
V. Developing Science into Products Chair: Kurt Brunden, PhD, University of Pennsylvania		
1:10 – 1:15	Session Overview Kurt Brunden, PhD, <i>University of Pennsylvania</i>	
1:15 – 1:35	Novel Approaches to Technology Transfer: Pharma-Academia Collaborations Robert Zivin, PhD, <i>University of Miami</i>	
1:35 – 1:45	Q&A	
1:45 – 2:05	Innovation in Tech Transfer and the Role of the Tech Transfer Office Todd Huffman, PhD, <i>The Scripps Research Institute</i>	
2:05 – 2:15	Q&A	
2:15 – 2:35	A Re-Understanding of How to Protect and use Intellectual Property Leslie Meyer-Leon, PhD, JD, <i>IP Legal Strategies Group PC</i>	
2:35 – 2:45	Q&A	
2:45 – 3:05	Break	
VI. What do Partners Look For? A Perspective from Pharma, Private Investors and Philanthropy Chair: Frank Longo, MD, PhD, Stanford University and Pharmatrophix		
3:05 -3:15	Introduction: Challenges in Securing Partnerships Frank Longo, MD, PhD, <i>Stanford University and Pharmatrophix</i>	
3:15 – 3:55	Panel Discussion: What do Partners Look For? Adrian Howd, PhD, Evotec AG Sanjeev Munshi, PhD, Merck & Co., Inc. Dennis Yamashita, PhD, GlaxoSmithKline Marco Baptista, PhD, The Michael J. Fox Foundation for Parkinson's Research	
3:55 – 4:10	Q&A	
4:10 – 4:15	Closing Remarks Howard Fillit, MD, <i>Alzheimer's Drug Discovery Foundation</i>	

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Funding for this conference was made possible in part by Cooperative Agreement UI3AG031125 from the National Institute on Aging.

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2014 ADDF AWARDS and SCHOLARSHIPS

Congratulations to all of the 2014 ADDF Young Investigator Scholarship and Award winners! These scholarships recognize the early achievements of talented young investigators and seek to encourage the career development of the next generation of research scientists in the field of drug discovery for neurodegenerative diseases. All winners receive free conference registration and the opportunity to present a poster. Outstanding Young Investigators and Award Winners also receive a travel stipend.

2014 ADDF OUTSTANDING YOUNG INVESTIGATOR AWARDS

Jesse Cochran, *University of Alabama at Birmingham, Birmingham, AL, USA*

Christopher Donnelly, *Johns Hopkins University, Baltimore, MD, USA*

Bethann Johnson, *Harvard NeuroDiscovery Center, Brigham and Women's Hospital, Boston, MA, USA*

Benjamin Rotstein, *Harvard Medical School and Massachusetts General Hospital, Boston, MA, USA*

Catherine Ward, *University of Massachusetts Medical School, Worcester, MA, USA*

2014 ADDF YOUNG INVESTIGATOR SCHOLARSHIPS

Vibhor Agrawal, *Clemson University, Clemson, SC, USA*

Kuntarat Arunrunchian, *Mahidol University, Bangkok, Thailand*

Narjes Baazaoui, *New York Institute for Basic Research, Staten Island, NY, USA*

Gerard Broussard, *University of California Davis, Sacramento, CA, USA*

Hsiang-Yu Micheal Chang, *China Medical University, Taichung, Taiwan*

Michele Frendo, *University of Southern California, Pasadena, CA, USA*

Ronak Gandhi, *University of Illinois Chicago, Chicago, IL, USA*

Archi Joardar, *University Of Arizona, Tucson, AZ, USA*

Beena Kadakkuzha, *Scripps Florida, Jupiter, FL, USA*

Maria Kawalec, *Mossakowski Medical Research Centre PAS, Warsaw, Poland*

Jana Löffler, *Technische Universität Dresden, Dresden, Saxony, Germany*

Maninder Malik, *University of North Texas Health Science Center, Fort Worth, TX, USA*

Dipan Patel, *University of Utah, Salt Lake City, UT, USA*

Federica Prati, *Italian Institute of Technology, Genova, Italy*

William Pryor, *Scripps Florida, Jupiter, FL, USA*

Gregory Remigio, *University of Utah, Salt Lake City, UT, USA*

Katie Ryan, *Brigham and Women's Hospital, Boston, MA, USA*

Reddy Ranjith Kumar Sama, *University of Massachusetts Medical School, Worcester, MA, USA*

Yuanli Song, *Vanderbilt University, Nashville, TN, USA*

Faraz Kazim Syed, *SUNY Downstate Medical Center/NYS Institute for Basic Research, Staten Island, NY, USA*

Koteswara Rao Valasani, *University of Kansas, Lawrence, KS, USA*

Rafael Vieira, *Simon Fraser University, Burnaby, BC, Canada*

Juwina Wijaya, *University of California, Los Angeles, CA, USA*

Qisheng Xin, *Albert Einstein College of Medicine, Bronx, NY, USA*

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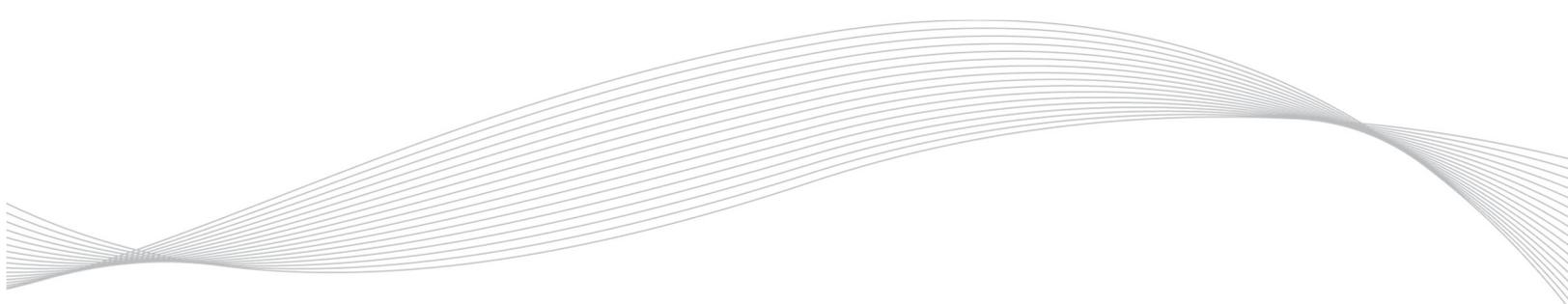
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CHAIRS AND SPEAKERS



BIOS AND ABSTRACTS

WELCOME NOTES

Howard Fillit, MD, Alzheimer's Drug Discovery Foundation



Howard Fillit, MD, a geriatrician, neuroscientist and a leading expert in Alzheimer's disease, is the founding Executive Director of the Institute for the Study of Aging (ISOA), an Estée Lauder family foundation founded in 1998, and the Alzheimer's Drug Discovery Foundation (ADDF), an affiliated public charity founded in 2004.

ISOA and ADDF share a common mission of accelerating drug discovery for Alzheimer's disease through venture philanthropy. Dr. Fillit has had a distinguished academic medical career at The Rockefeller University and The Mount Sinai School of Medicine where he is a clinical professor of geriatrics and medicine and professor of neurobiology.

He was previously the Corporate Medical Director for Medicare at New York Life, responsible for over 125,000 Medicare managed care members in five regional markets. He is the author or co-author of more than 250 scientific and clinical publications, and is the senior editor of the leading international Textbook of Geriatric Medicine and Gerontology. Dr. Fillit has received several awards and honors including the *Rita Hayworth Award for Lifetime Achievement* from the Alzheimer's Association. He also serves as a consultant to pharmaceutical and biotechnology companies, health care organizations and philanthropies.

PLENARY LECTURE

Frank Sams-Dodd, PhD, DSc, Willingsford Ltd



Frank Sams-Dodd holds an MSc degree in ethology from Copenhagen University, a PhD degree from Cornell University in integrative neurobiology and physiology, and an honorary doctoral degree in medicine from Copenhagen University for his schizophrenia research. Dr. Sams-Dodd has previously been research fellow at H. Lundbeck A/S in the area of CNS disorders, particularly involved in schizophrenia and Parkinson's disease research, co-founder of a company offering university-based contract research and licensing towards the pharmaceutical industry; Director of Physiology at Amylin Pharmaceuticals, Inc. in San Diego in the area of metabolic disorders; Head of Psychopharmacology at Boehringer Ingelheim Pharma, Germany with responsibility for the pre-clinical drug discovery in Alzheimer's Disease and psychiatry; and VP pre-clinical research at Bionomics Ltd., an Australian biotech company and CEO of Neurofit SAS, their pre-clinical CRO facility in Strasbourg, France. In 2008, Dr. Sams-Dodd co-founded and became CEO of Willingsford Ltd., a company developing a novel first-in-class product for advanced wound care.

Functional Approaches to CNS Drug Discovery and the Potential for Drugs with Multiple Targets as a Mechanism of Action

Frank Sams-Dodd

Willingsford Ltd, Southampton Hampshire, United Kingdom

Target-based drug discovery has been the dominant approach in the pharmaceutical industry for the past 20 years, but it has in recent years been realized that, while the approach can be highly effective for some programs, it cannot be applied widely to all drug discovery programs. The purpose of the presentation is to review the main approaches to drug discovery, their strengths and weaknesses and what can be achieved by screening for functional changes at the cell/systems level and using drugs affecting multiple targets.

WELCOME NOTES

Lorenzo Refolo, PhD, National Institute on Aging



Dr. Lorenzo M. Refolo received a BSc from the University of Connecticut, and was awarded a PhD 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 has been Program Director in the Neurodegeneration Cluster at the National Institute of Neurological Disorders and Stroke (NINDS) where his major responsibility was the management of a portfolio of grants on ALS, Alzheimer's and Parkinson's diseases and Vascular Cognitive Impairment. In 2009, Dr. Refolo joined NIA, the Division of Neuroscience, Dementia Branch.

Preclinical Therapeutics Development for Neurological Disorders: Funding & Resources

Lorenzo Refolo

National Institute on Aging, Bethesda, MD, USA

Dr. Refolo will give an overview of the National Institute on Aging's Alzheimer's disease translational research program and the current NIA funding opportunities for drug discovery and preclinical drug development. He will also highlight translational research resources at the greater NIH-level and provide practical advice on how the extramural community can best take advantage of the above funding opportunities and resources.

Patricia Ann Walicke, MD, PhD, National Institute of Neurological Disorders and Stroke



Dr. Patricia Walicke is the Medical Officer in the Office of Translational Research at NINDS where she will be responsible for providing clinical input into translational activities, will contribute to first in human clinical trials and will support translation efforts in the NINDS intramural program. Dr. Walicke has more than 20 years of experience in the pharmaceutical development, starting as an investigator in clinical trials and then moving to biotechnology. She worked at Quintiles, Elan Pharma, and Genentech, before entering the start-up company arena. She participated in translational science and built clinical departments at three small companies, Rinat Neurosciences, Avidia Pharma, and Oxigene. For the last five years prior to joining NIH, she served as a consultant to multiple small and virtual biotechnology companies in the San Francisco area. She has worked on projects in a variety of neurologic indications including Alzheimer's disease, multiple sclerosis, pain, peripheral neuropathy, epilepsy, stroke, Down syndrome, Duchenne muscular dystrophy, Eaton Lambert syndrome and neuronal ceroid lipofuscinosis.

Dr. Walicke received her bachelor's degree from MIT, an MD degree from Harvard Medical School and performed her PhD doctoral training with Dr. Paul Patterson at Harvard University on development of sympathetic neurons. Prior to industry, she was an assistant professor at UCSD and subsequently founded a private neurology practice. She has held adjunct appointments at the Salk Institute, Emory University, Mercer University School of Pharmacy, and UCSF.

Preclinical Therapeutics Development for Neurological Disorders: Funding & Resources: NINDS Accelerates Therapeutic Discovery and Development for Neurodegenerative Diseases

Patricia Ann Walicke

National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA

The National Institute of Neurologic Disorders and Stroke (NINDS) is a leading NIH funding source for dementia research, including vascular dementia, Lewy body dementias (PDD, DLB), frontotemporal dementia and other tauopathies, and plays a supporting role in Alzheimer's disease research. In addition, it is the lead NIH institute for neurodegenerative disorders such as Parkinson disease, Huntington's disease and ALS. The Office of Translational Research within the NINDS currently has the following funding programs that aim to provide a breadth of opportunities for academic investigators and small businesses to engage in the spectrum of work, beginning with assay development through to initial test of clinical candidate in human trials:

1. The U01 Cooperative Translational Research Program (a milestone-driven funding mechanism)
2. Blueprint Neurotherapeutics (a virtual pharma network)
3. The SBIR (Small Business Innovation Research) Program

The emerging priorities of the NINDS OTR office are to:

- Ensure that therapeutic development is partnered with the development of mechanistic biomarkers;
- Facilitate deeper understanding of the mechanism of action of the therapeutic candidate, for example by the greater use of imaging;
- Encourage work on diseases that do not have predictive animal models of efficacy;
- Ensure that programs meet criteria for experimental rigor and yield robust results;
- Encourage the use phase 0 clinical trials via exploratory Investigational New Drug (eIND) route.

Additionally, there will be emphasis going forward on engaging other stakeholders, such as pharma, biotech, venture capital, and patient organizations to ensure that projects in the office's portfolio have been appropriately de-risked to ensure downstream investments, which will accelerate getting the much-needed therapies to patients suffering from neurological disorders.

SESSION I

Introduction to Small Molecule Chemistry for Biologists

Chair: D. Martin Watterson, PhD, Northwestern University

Session Overview

Themes in Successful Prior Art for Novel Small Molecule Discovery in CNS Disorders

D. Martin Watterson, PhD, *Northwestern University*

Synthetic Chemistry Fundamentals in Lead Compound Refinement

Jeff Pelletier, PhD, *Fox Chase Chemical Diversity Center, Inc.*

Natural Products as Drug Starting Points

Frank Koehn, PhD, *Pfizer Inc.*

SESSION CHAIR

D. Martin Watterson, PhD, Northwestern University



Dr. Daniel Martin Watterson holds the John G. Searle Endowed Chair Professorship at Northwestern University where he is a Professor in the Department of Molecular Pharmacology & Biological Chemistry at the Feinberg School of Medicine. Dr. Watterson has worked successfully with major pharmaceutical and biotech companies in diverse areas of drug discovery, participated actively in bringing new drug candidates to clinical development, served on the Board of Directors for technology companies, founded profitable commercial enterprises with success in deliverables and timelines, and assisted colleagues and various government agencies with science and technology development. At Northwestern, he has served as a Department Chair, Co-Director of the Graduate Curriculum in Drug Discovery and Chemical Biology and a University Center, and founding director of the Drug Discovery Program.

Before moving to Northwestern University, Dr. Watterson held faculty positions at The Rockefeller University, where he was an Andrew Mellon Fellow, and at Vanderbilt University Medical Center, where he was Professor of Pharmacology and Howard Hughes Investigator. His doctoral training in chemical sciences was at Emory University, followed by postdoctoral training in biochemistry and bioorganic chemistry at Duke University Medical Center where he was supported by a National Research Service Award from the National Institutes of Health.

Themes in Successful Prior Art for Novel Small Molecule Discovery in CNS Disorders

D. Martin Watterson

Northwestern University, Chicago, IL, USA

This session is planned as an introduction for biologists to the concepts and principles behind the use of synthetic chemistry as applied to drug discovery and early preclinical drug development. The depth of experience and emergent general themes are greater for organic molecules compared to macromolecules, so the limited time of the session will focus on small molecules. The starting points for most discovery and development efforts are usually small compounds emerging from synthetic organic chemistry programs or from natural products as starting materials. Therefore, the two in-depth presentations on synthetic chemistry and natural products as starting points will provide case studies that demonstrate the trends and themes that often characterize such campaigns.

The employment of medicinal chemistry in drug discovery begins at the early target identification and validation stage. Compounds used at this stage are usually chemical tools for biological studies and help prioritize which macromolecules are potential discovery targets. There are usually fewer demands at this early stage placed on the in vivo relevant metabolism and safety properties of the tool compounds. However, chemical tool compounds designed for in vivo use can be useful starting points for the later stage drug discovery lead compound attainment. A major question at the early stage is the question of target “druggability”. The pharmacologist wants to know if the chemical tool is able to generate a desired pharmacodynamic response, thereby suggesting the potential of therapeutic intervention success at later stages. The chemist wants to know if there are tractable, off-the-shelf chemistries that can be used to generate lead compounds amenable to refinement and optimization as the campaigns moves into late discovery and early stage development. The early discovery stage is also where specialization becomes key, with CNS drug discovery presenting special challenges. For example, what is the potential for a hit or lead compound to be refined into a drug candidate that retains or improves target affinity and selectivity while attaining the required blood:brain barrier penetrance and avoiding metabolic liabilities that contribute to clinical trial issues? The overview will highlight how discovery engine design using contemporary approaches can assist in risk reduction at later stages while retaining the potential for innovation. The general themes will be expanded upon in the presentations on synthetic chemistry fundamentals in lead compound refinement and on natural products as a starting point. These two presentations will use case studies for explicit didactic points. The goal of the session is to make biologists aware of the potential approaches and the challenges they can address by consideration of chemistry at the front end of the drug discovery and development campaign.

Jeff Pelletier, PhD, Fox Chase Chemical Diversity Center, Inc.



Dr. Jeff C. Pelletier received his PhD in chemistry from the University of Pennsylvania and has over 25 years in the pharmaceutical industry as a medicinal chemist, including 13 years with Wyeth Research and 2 years with Symphony Pharmaceuticals. He is an experienced leader of large, multidiscipline drug discovery teams in neuroscience, endocrinology, cardiovascular and inflammation therapeutic areas. He has expertise in enabling technologies including high-throughput screening, fragment based drug discovery, ligand and structure based discovery, analytical chemistry, multi-step synthesis, parallel synthesis, data management and ADME evaluation. His publication record includes 26 peer-reviewed articles, 38 presentations and invited lectures, 24 issued/pending US patents.

Dr. Pelletier currently serves as a Research Fellow at Fox Chase Chemical Diversity Center, Inc. and holds an Adjunct Professorship at the Feinberg School of Medicine, Northwestern University, where he collaborates on medical issues related to critical care medicine and neurodegeneration.

Synthetic Chemistry Fundamentals in Lead Compound Refinement

Jeff Pelletier

Fox Chase Chemical Diversity Center, Inc., Doylestown, PA

In recent years a large portion of drug discovery research has shifted to small biotech operations, non-profit organizations, academic institutions and government labs. The transition has placed additional knowledge demands on scientists engaged in pharmaceutical research outside of their traditional functions. A primary challenge to the biologist is a broader understanding of small molecule chemistry in a drug discovery environment. Small molecule drug discovery remains a chemo-centric paradigm with structural design and synthesis at the core of this process. Central nervous system (CNS) agents require properties that allow delivery to the biological target (ADME) in conjunction with intrinsic interaction with the biological target leading to pharmacological efficacy. Both properties can be simultaneously optimized by the choice of structural modifications performed on small molecule hits and/or leads that promote appropriate molecular interactions with ADME barriers and the biological target. The desired result is a molecule with a balance of bioavailability and intrinsic target properties that lead to disease modification. The role of chemical sciences is an essential part of this strategy. In this talk a discussion of structural design strategies and synthetic plans in the drug discovery process and their application to lead generation, lead optimization and development candidate selection will be discussed. Enabling technologies such as high-throughput screening (HTS), fragment based drug discovery (FBDD), ligand binding optimization, structural design and synthesis will be discussed as well. Finally a brief discussion of process chemistry and the role of Chemical Manufacturing and Controls (CMC), essential for the transition to drug development and manufacturing, will conclude the presentation.

Frank Koehn, PhD, Pfizer Inc.



Dr. Frank E. Koehn is Research Fellow and Head of the Natural Products Laboratory at Pfizer Worldwide R&D. He obtained his BS degree in chemistry from Butler University, Indianapolis Indiana in 1977, and did his PhD research on marine red tide neurotoxins at the University of Wisconsin, Madison, USA. Following postdoctoral work in plant natural products at the University of Pennsylvania, Dr. Koehn joined the Harbor Branch Oceanographic Institution in Fort Pierce, Florida, USA, where he spent the next decade identifying biologically active molecules from marine macro and micro-organisms.

Intrigued by the therapeutic potential of natural product-based drug candidates, Dr. Koehn joined the Natural Products and Analytical Chemistry program at Lederle Laboratories in 1994, which subsequently became Wyeth Research.

In 2010 he joined Pfizer as Natural Products Laboratory head. At Pfizer, Dr. Koehn's research group is focused on the discovery and application of microbial natural products to address unmet medical need.

Natural Products as Drug Starting Points

Frank Koehn

Pfizer Inc., Groton, CT

Natural products derived from plants, microbes and marine organisms are an unsurpassed source of lead structures for drug discovery. It is now apparent that these molecules offer a means of addressing the previously “undruggable” target space that is often associated with neurodegenerative diseases. However, natural products are often difficult to advance in a lead development sense because of their complex chemical structures and limited availability. Chemical synthesis and biosynthetic engineering of the producing host organisms now offer means to modify natural product leads in new ways that address these issues head-on. This talk describes the current role of natural products in lead generation and goes on to describe cases where synthetic and biosynthetic medicinal chemistry have been effectively used to advance natural product drug candidates.

SESSION II

Embarking on a Drug Discovery Campaign

Chair: Kalpana Merchant, PhD, Eli Lilly and Company

Session Overview

De-risking Parkinson's Disease Drug Development via Optimal Target Validation and Decision-driving Biomarkers

Kalpana Merchant, PhD, *Eli Lilly and Company*

Using Chemical Probes for Target Validation and to Understand Target Liability

Jian Jin, PhD, *University of North Carolina at Chapel Hill*

Assembling the Right Interdisciplinary Team From the Beginning

Julie Frearson, PhD, *BioFocus*

SESSION CHAIR

Kalpana Merchant, PhD, Eli Lilly and Company



Dr. Kalpana Merchant was named the Chief Scientific Officer for Translational Science in Lilly Discovery in January 2010. She played the leadership role in the design of the Translational Science department. The overall objective of Translational Science is to provide drug targets linked to disease biology and biomarkers to facilitate drug discovery, development and patient tailoring for all therapeutic areas of interest to Lilly. To achieve this objective, Dr. Merchant implemented a multidisciplinary approach involving human genetics, functional genomics & cellular research, bioinformatics, molecular pathology, imaging as well as mass spectrometric bioanalytics to gain insights into disease biology at a molecular level. She provides direct oversight of the Translational Science portfolio supporting neuroscience drug discovery research.

Dr. Merchant received her doctorate in neuropharmacology from the University of Utah in 1989. Following a postdoctoral research fellowship at University of Washington, she was appointed as an Assistant Professor of Psychiatry at University of Washington. She was recruited to Lilly in 2003 from a position of Senior Research Advisor and Fellow at Pharmacia Corp., where she had contributed to CNS drug discovery research for 10 years. Dr. Merchant's own laboratory's has been focused on elucidating disease mechanisms associated with Parkinson's disease, Alzheimer's disease and neuropsychiatric disorders and connecting the biology of drug targets to disease biology. She is engaged in the wider scientific community via her service on NIH Study Sections, NIH or IOM workshops and Advisory Panels, scientific advisory board for The Michael J Fox Foundation for Parkinson's Research as well as membership in several national and international professional societies.

De-risking Parkinson's Disease Drug Development via Optimal Target Validation and Decision-driving Biomarkers

Kalpana Merchant

Eli Lilly and Company, Indianapolis, IN, USA

It is well recognized that Parkinson's disease is a complex trait syndrome. There is a high degree of heterogeneity in clinical symptoms, etiology, pathophysiology as well as progression course. Therefore, not surprisingly, patient responses to marketed and investigational drugs are also heterogeneous and not predictable. This has led to failures of clinical trials of several investigational drugs. This talk will focus on translational science approaches directed at addressing gaps in key factors that contribute to clinical failures of novel therapeutics: (a) wrong therapeutic target, (b) wrong dose/dosing regimen and (c) wrong patient population. A road map based in integrated applications of genetic/genomic, imaging, physiological, or biochemical biomarkers will be discussed to demonstrate the impact of timely integration of translational science to increase the probability of technical success.

Jian Jin, PhD, University of North Carolina at Chapel Hill



Dr. Jian Jin is an Associate Professor in the Division of Chemical Biology and Medicinal Chemistry and Department of Pharmacology, an Associate Director of Medicinal Chemistry in the Center for Integrative Chemical Biology & Drug Discovery, and a Member of Lineberger Comprehensive Cancer Center at the University of North Carolina - Chapel Hill (UNC-CH).

His current research interests include discovering chemical probes for histone methyltransferases and functionally selective ligands of G protein-coupled receptors. Prior to joining UNC-CH in 2008, Dr. Jin had over 10 years of drug discovery experience at GlaxoSmithKline, where he had most recently served as a Manager of Medicinal Chemistry from 2003 to 2008. Dr. Jin has published 77 peer-reviewed papers and is an inventor of nine issued U.S. patents and 37 published PCT patent applications. He also delivered over 40 invited talks.

Using Chemical Probes for Target Validation and to Understand Target Liability

Jian Jin

University of North Carolina, Chapel Hill, NC, USA

Chemical probes are valuable tools for investigating biological functions of proteins of interest and for assessing the potential of these proteins as therapeutic targets. Well-characterized chemical probes will permit biological and disease hypotheses to be tested in cell-based and animal models with high confidence. In addition, chemical probes can be used for assessing potential mechanism-based toxicity. In this talk, I will present our recent progress on discovering chemical probes of histone methyltransferases and functionally selective ligands of G protein-coupled receptors.

Julie Frearson, PhD, BioFocus



Following her BSc in Biochemistry, Dr. Frearson studied signal transduction in vascular endothelial cells during her PhD at King's College London. During the period 1994 to 1998 she worked as a postdoctoral fellow at the Babraham Institute, Cambridge UK dissecting the role of tyrosine phosphatases in T-cell signalling. She then joined Cambridge Drug Discovery where she led the cell signalling group and engaged in hit discovery programs across a range of enzyme classes.

Dr. Frearson became part of BioFocus in 2001 and after two years of leading a department engaging in hit discovery and hit-to-lead programs for kinases and ion channels, became Director of Biology. In this role she was responsible for both the scientific and commercial leadership of 30 staff engaging in molecular pharmacology and in vitro ADME.

In 2005 Dr. Frearson joined the University of Dundee (UK) to enable their translational drug discovery ambitions. As Professor of Biotechnology, she co-founded and developed operations at The Drug Discovery Unit at Dundee. She directed translational drug discovery portfolios across a range of neglected diseases and for novel targets and mechanisms addressing oncology, rare genetic disease and stem cell fate. Dr. Frearson is a strong advocate of early translational drug discovery from academic concepts and has served as SULSA Director of Translational Biology for Scotland and on MRC and Wellcome Trust Committees. She is co-author of more than 40 peer-reviewed publications.

Following a move to the USA, Dr. Frearson joined BioFocus in 2011 in a Scientific Alliances role. She now leads BioFocus' venture into new partnerships with the non-profit sector, including academic institutions and patient foundations and has overall responsibility for new business development globally.

Assembling the Right Interdisciplinary Team from the Beginning

Julie Frearson

BioFocus, USA

Logic dictates that the extreme challenges of drug discovery- designing and developing a single, simple organic molecule to be efficacious and safe across a patient population will inevitably require the hearts and minds of a team effort. This session will be targeted at academic scientists who wish to pressure-test and translate their therapeutic hypothesis and will describe the ideal profile of the multitude of scientific disciplines involved from early target validation through to first in human studies. Using case studies we will discuss the science, processes and cultural mix needed for a successful drug discovery effort and, critically, provide practical guidance on accessing the appropriate expertise.

SESSION III

Drug Discovery: From Screening to Clinical Candidate

Chair: Edward Spack, PhD, Fast Forward, LLC

Session Overview

New Trends in High Throughput Screening (HTS): Rapid and Inexpensive Discovery of Natural Product-like Molecules for Probe and Drug Development

Thomas Kodadek, PhD, *Scripps Florida*

Compound Optimization after HTS: From Hit to Lead

Kurt Brunden, PhD, *University of Pennsylvania*

Designing a Therapeutic Animal Study: Employing Translatable Biomarkers

Manfred Windisch, PhD, *NeuroScios - Neuroscience Optimized Solution*

Requirements for an IND and Early Considerations

Edward Spack, PhD, *Fast Forward, LLC*

When Should You Engage a Contract Research Organization?

Katya Tsaïoun, PhD, *Pharma Launcher*

ADDF ACCESS Program/Closing Remarks

Rachel Lane, PhD, *Alzheimer's Drug Discovery Foundation*

Thomas Kodadek, PhD, Scripps Florida



Dr. Thomas Kodadek received his BS in Chemistry at the University of Miami (FL) in 1981 and his PhD in Organic Chemistry from Stanford University in 1985. He then pursued post-doctoral studies in the laboratory of Prof. Bruce Alberts at the University of California, San Francisco Medical School from 1985-1987. In the fall of 1987 he joined the faculty of Chemistry & Biochemistry at the University of Texas at Austin, rising to the rank of full professor. In 1998, he moved to the University of Texas Southwestern Medical Center in Dallas where he served as Professor of Internal Medicine and Molecular Biology as well as the Director of the Division of Translational Research. In June, 2009, Dr. Kodadek moved to the Scripps Research Institute campus in Jupiter, FL where he is currently Professor of Chemistry & Cancer Biology. He was a recipient of the NIH Director's Pioneer Award in 2006.

Dr. Kodadek works in the field of chemical biology, which involves the development of chemical tools to monitor and manipulate important processes in biology and medicine. His laboratory has also made important contributions to our understanding of how genes are rearranged and expressed. More recently, Professor Kodadek has focused on the development of novel diagnostic and therapeutic tools for the treatment of immune diseases and cancers. This work was recognized in 2006 by a prestigious NIH Director's Pioneer Award for "exceptionally creative research". Opko, a Miami biotechnology company, has established a laboratory in Jupiter for the discovery of novel diagnostic markers for cancer, autoimmune and neurological diseases using the methods developed in the Kodadek laboratory.

New Trends in High Throughput Screening (HTS): Rapid and Inexpensive Discovery of Natural Product-like Molecules for Probe and Drug Development

Thomas Kodadek

Scripps Florida, Jupiter, FL, USA

Nowadays, most therapeutic candidates are mined from libraries or compound collections via some sort of high-throughput screening assay. While powerful, this technology has numerous limitations, include expense and the isolation of hits with unknown selectivity for the target. Moreover, the compounds present in most screening collections are not ideal, both with respect to their molecular properties and their ease of synthesis. This lecture will discuss the development of an alternative screening strategy. This involves creating large libraries of natural product-like molecules displayed on hydrophilic microbeads. Hundreds of thousands of beads are then exposed to a labeled target of interest in the presence of a large excess of unlabeled competitor molecules. Beads that retain the labeled target under these conditions are isolated and the structure of the hit is determined by tandem mass spectrometry. We provide examples of the utility of this approach to probe and lead discovery for both soluble protein targets as well as integral membrane receptors.

Kurt Brunden, PhD, University of Pennsylvania



Dr. Kurt R. Brunden is Director of Drug Discovery and Research Professor in the Center for Neurodegenerative Disease Research (CNDR) at the University of Pennsylvania, where he oversees drug discovery programs in the areas of Alzheimer's disease (AD), frontotemporal lobar degeneration and Parkinson's disease. Prior to joining CNDR in 2007, Dr. Brunden was an executive in the biotechnology sector, where he served as VP of Research at Gliatech, Inc. and later as Sr. VP of Drug Discovery at Athersys, Inc. In these positions, he initiated and managed drug discovery programs in AD, cognitive enhancement, schizophrenia, inflammation, metabolic disease and cancer.

Prior to his time in industry, Dr. Brunden was an NIH-funded faculty member within the Biochemistry Department at the University of Mississippi Medical Center, with a research focus on the regulation of myelination. He obtained his BS degree from Western Michigan University, with dual majors of Biology and Health Chemistry, and his PhD in Biochemistry from Purdue University, with a post-doctoral fellowship at the Mayo Clinic.

Compound Optimization after HTS: From Hit to Lead

Kurt Brunden

University of Pennsylvania, Philadelphia, PA, USA

The completion of high-throughput screening (HTS) of compound libraries often triggers a series of subsequent drug discovery activities that include secondary testing of initial HTS hits, selection of preferred chemotypes, and initiation of medicinal chemistry efforts. As chemical analogues are generated, they must be evaluated not only for their potency at the desired drug target, but also for key attributes such as aqueous solubility, pharmacokinetic behavior, pharmacological safety and, in the case of CNS drug targets, blood-brain barrier permeability. This session will provide examples of assays that can be established and utilized in academic centers to gain a better understanding of these key compound characteristics before progressing to more advanced toxicological and efficacy testing of lead candidates in animals.

Manfred Windisch, PhD, NeuroScios - Neuroscience Optimized Solutions



Dr. Manfred Windisch founded JSW Lifesciences GmbH, an independent international contract research organization located in Grambach, Austria in the year 1999. JSW specializes on research about neurodegenerative disorders and in his current capacity Dr. Windisch focuses on pharmacological studies of novel compounds for treatment Alzheimer's, Parkinson's disease and stroke, from molecular screening up to *in vivo* model systems, from early screening to phase 3 of clinical studies. In the year 2012 his company was merged with the international CRO QPS, where he continues his work in the function as head of global neuroscience, to further profile the company's expertise in that field.

After graduation from the University of Graz in 1985 he spent several years heading a neurobiology group at the University with research in the field of brain metabolism and animal model development after which he was involved for many years in University and industrial research programs in Europe, North America and Asia. He established a global network of research collaborations and stimulated intensive scientific information exchange. Besides his involvement in basic research on neurotrophic and neuroprotective factors, he spearheaded several international clinical studies in Alzheimer's disease. He is a highly active member of the scientific community and has authored about 100 original research articles in peer-reviewed journals. He is organizing conferences in the field of drug development for treatment of neurodegenerative diseases and is one of the executive organizers of the ADPD conference. As a member of several scientific advisory boards he is helping to coordinate preclinical and clinical research activities in that field on an international level. He is also active in creating improved models of neurodegenerative diseases, which should allow early drug testing with a higher predictive value.

In August 2013 he founded a new company "NeuroScios – Neuroscience Optimized Solutions" and took over the position as a CEO there. This company is highly specialized in consulting for complete drug development programs in neurological indications and it provides premier expertise in clinical trials in dementia (AD; MCI and others) as well as cerebro-vascular disorders (stroke). The basis for the quality of his consulting are 35 years of experience in AD-research and about 15 years of intense work with disease models, practically being exposed to all types of treatment approaches for AD.

Designing a Therapeutic Animal Study: Employing Translatable Biomarkers

Manfred Windisch

NeuroScios - Neuroscience Optimized Solutions, Graz, Austria

On one hand there is no naturally occurring animal model of AD available, but on the other hand there is a manifold of transgenic or induced rodent models available that can be used for testing of new treatment approaches. The first step is certainly the choice of the right model for the particular new compound and the proposed mode of action. The careful planning of an experiment includes power analysis, knowledge about PK, dosing schedule, selection of the right age group and the definition of the outcome variables. The experience of the past has shown that biomarkers like A-Beta peptides or tau/ptau in CSF, or even brain plaque load, can be well translated into clinical read outs, the most critical issue is the translation of cognitive improvement, therefore any study should include behavior, ideally using different testing paradigms. The model should show a correlation between pathological changes and cognition over time with ongoing "disease progression", and ideally there should be a positive control available demonstrating that target engagement is correlated to functional improvement. Modern imaging techniques, like high resolution MRI allow performing longitudinal treatment trials to explore time course of therapeutic effects, again including important biomarkers like amyloid plaques or brain atrophy. At the end the careful analysis and interpretation of the animal data will allow higher predictive value. Ideally defined and already published standards for such studies should be applied.

SESSION CHAIR

Edward Spack, PhD, Fast Forward, LLC



Dr. Edward Spack received his doctoral degree from The Johns Hopkins University and his postdoctoral fellowship in cellular immunology at Stanford University. He worked in Bay area biotech companies for 14 years developing therapies for autoimmunity, cancer, and infectious disease spanning discovery and preclinical development through Phase III trial support. At SRI International, Dr. Spack directed the PharmaSTART program, a consortium of SRI, Stanford, UC Berkeley, UCSD, and UCSF chartered to support translational development. His responsibilities included designing preclinical development plans for academic researchers, foundations, NIH programs, and start-up companies. He consulted with the NIH translational core services committee and several individual NIH institutes on preclinical development and served as an advisor on the NIH Regional Centers of Excellence for Biodefense and Emerging

Infectious Diseases Produce Development Working Group. As Senior Director of Business Development for SRI's Bioscience Division, Dr. Spack was responsible for alliance management, in-licensing, and out-licensing of drug candidates. He has served on scientific advisory boards, grant review boards, or national board of directors for several foundations, and is currently a managing director at Fast Forward LLC, supporting a translational development program advancing therapeutics for the prevention/reversal of neurodegeneration in multiple sclerosis in partnership with EMD Serono.

Requirements for an IND and Early Considerations

Edward Spack

Fast Forward, LLC, San Francisco Bay, CA, USA

In the United States, an Investigational New Drug (IND) application must be submitted to the FDA before a drug candidate can be tested in humans. An IND follows a proscribed format and documents the drug discovery and preclinical development activities that support the basis for testing in a specified therapeutic application, define the drug composition, and demonstrate the level of safety. A new IND is required for a new indication, change in route of drug administration or dosage, or change in patient population. Each IND includes information on three broad areas: animal pharmacology and toxicology studies; chemistry and manufacturing processes; clinical protocol and investigator information. Previous talks will cover studies of drug absorption, distribution, metabolism, and excretion (ADME); this presentation will include a discussion of Good Laboratory Practices (GLP) and the formal components of an IND Animal Pharmacology and Toxicology section. The Chemical, Manufacturing, and Control (CMC) section characterizes the chemical composition, manufacturing methods, potency, purity, stability, and controls used for manufacturing the drug substance and the drug product (active ingredient and excipients) performed according to Good Manufacturing Practices (GMP). The presentation will also discuss differences between investigator initiated and sponsor initiated INDs, pre-IND meetings, and other regulatory issues. Preparing for an IND is not simply a matter of following a recipe or coloring within the lines- there are strategic considerations that should be part of the earliest planning for a drug candidate. A Target Product Profile (TPP) provides a good guideline for drug optimization and testing. As part of this early stage, in addition to proof of concept, the TPP disciplines drug developers to consider proof of relevance, focusing on clinical need and competing alternative approaches. Coordinating the safety testing and manufacturing, as well as the models that inform dosing and other aspects of clinical trial design requires careful project management. In summary, developing and executing IND-enabling studies and moving a discovery to clinical trial requires problem solving and teamwork, and the most important early consideration is to begin with the end in mind.

Katya Tsaïoun, PhD, Pharma Launcher



Dr. Tsaïoun is a widely recognized expert in preclinical drug-discovery research. Her book, *ADMET for Medicinal Chemists*, was published in 2011 by Wiley & Sons. Dr. Tsaïoun serves on the scientific review boards of the National Institute of Aging, the Alzheimer's Drug Discovery Foundation, and the International Rett Syndrome Foundation. Dr. Tsaïoun is regularly interviewed by trade publications such as *Genetic Engineering News* and *Drug Discovery Technology*, and is invited to speak at conferences on the topics of early toxicity assessment, building productive R&D teams, and entrepreneurship.

Before founding Pharma Launcher, Dr. Tsaïoun was Chief Scientific Officer at Cyprotex, the world's largest contract research organization specializing in ADME Tox. Cyprotex is a publicly traded, UK-based company with laboratories in the US and UK. Dr. Tsaïoun joined Cyprotex subsequent to Cyprotex's 2010 acquisition of Apredica, where she was a co-founder and President. At Cyprotex, Dr. Tsaïoun managed scientific strategy and strategic alliances, particularly focusing on the ADME Tox technologies developed at Apredica, and those which Apredica acquired from Cellumen. Apredica opened business in 2006. In four years Dr. Tsaïoun grew Apredica from 1.5 to 12 FTEs. Apredica initially focused on preclinical ADME contract research, then expanded to become an early leader in the *in vitro* toxicology market. Prior to founding Apredica, Dr. Tsaïoun managed the ADME programs for NitroMed, and before that, Surface Logix.

Dr. Tsaïoun earned her BS/MS degree in solid-state chemistry from the Leningrad Institute of Technology, and her PhD from Tufts University. Her PhD thesis on 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.

When Should You Engage a Contract Research Organization? Considerations Related to Capabilities, Size, and Stage of Drug Discovery Program

Katya Tsaïoun

Pharma Launcher, Boston, MA, USA

Reducing attrition at later stages of development is a top concern for most pharmaceutical industry executives and academic leaders. Identifying potential liabilities at an early stage in drug discovery has proven to reduce the likelihood of late stage failures. Which activities are most appropriate to handle in-house and which to outsource? Which CROs add the most value? Who should be involved in managing such partnerships? The CRO industry has matured and is undergoing restructuring. It is a very fragmented space with hundreds of small specialty shops and a few well-known giants. Appropriate use of CROs at each stage of a drug discovery program may mean the difference between success and failure. Examples of successful leveraging of CRO capabilities with internal resources will be presented.

Rachel Lane, PhD, Alzheimer's Drug Discovery Foundation



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

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

She is a member of the Society for Neuroscience and the New York Academy of Sciences and has published numerous first authored research publications and reviews in peer reviewed journals.

WELCOME NOTES

Diana Shineman, PhD, Director of Scientific Affairs, Alzheimer's Drug Discovery Foundation



Diana Shineman, PhD is the Director for Scientific Affairs at the Alzheimer's Drug Discovery Foundation, where she develops and manages the Foundation's drug discovery and development grant programs and strategic initiatives. Combining scientific and business expertise, the ADDF manages its research funding portfolio to balance risk, stage of development, and drug target mechanism of action, ensuring that grants meet key milestones before securing follow-on funding. As a measure of success, projects funded by the ADDF have gone on to garner nearly \$3 billion in follow-on funding. The ADDF also works strategically with foundations, government and industry partners to tackle unmet needs in the field. As an example of such an initiative, Dr. Shineman led an interdisciplinary effort to standardize animal model study design to improve research efficiency and translatability.

Diana joined the ADDF in 2008. She earned a PhD in Cell and Molecular Biology from the University of Pennsylvania working in the Center for Neurodegenerative Disease Research led by Drs. Virginia Lee and John Trojanowski. She also worked as an Editorial Intern for the Journal of Clinical Investigation and was an active member of the Penn Biotechnology Group. Diana received a BA in Biology with a Nutrition concentration from Cornell University, where she was named a Howard Hughes Undergraduate Research Scholar. In addition to maintaining various professional memberships, Diana has also authored numerous articles and peer-reviewed publications.

PLENARY LECTURE

Richard Silverman, Northwestern University



Dr. Richard B. Silverman received his BS degree in chemistry from Penn State in 1968 and his PhD degree in organic chemistry from Harvard in 1974 (with time off for a two-year military obligation from 1969-1971). After two years as a NIH postdoctoral fellow with Robert Abeles in enzymology at Brandeis University, he joined the chemistry faculty at Northwestern. In 1986 he became Professor of Chemistry and Biochemistry.

In 2001 he became the McCormick Professor of Teaching Excellence, and since 2004 he has been the John Evans Professor of Chemistry. He is the inventor of the blockbuster drug Lyrica™. Recent awards include the 2009 Perkin Medal, induction into the American Chemical Society (ACS) Medicinal Chemistry Hall of Fame (2009), the E.B. Hershberg Award for Important Discoveries in Medicinally Active Substances from the ACS (2011), Fellow of the ACS (2011), Sato Memorial International Award of the Pharmaceutical Society of Japan (2012), BMS-Smissman Award of the ACS (2013), the Centenary Prize of the Royal Society of Chemistry (2013), and the Excellence in Medicinal Chemistry Prize of the Israel Chemical Society (2014). He has published 320 research articles, holds 49 domestic and foreign patents, and has written four books.

The Story of Lyrica: Academic Discovery to Commercial Success

Richard Silverman

Northwestern University, Chicago, IL, USA

This lecture will describe the approach that was taken to design inhibitors of an enzyme that was found to be important for the treatment of epilepsy. The rationale and science behind the inhibitor design will be discussed that led to the discovery of Lyrica. The process involved in taking a discovery from an academic laboratory to an industrial partnership and on to commercialization also will be described. The properties of Lyrica that led to its success as a blockbuster drug for the treatment of fibromyalgia, diabetic neuropathy, postherpetic neuralgia, pain from spinal cord injury, epilepsy, and (in Europe) generalized anxiety will be highlighted.

SESSION IV

Strategies for Challenging CNS Targets – Case Study Examples

Chair: Marcie Glicksman, PhD, Harvard NeuroDiscovery Center

Session Overview

Case Study: From Bench to High Throughput Screen

Marcie Glicksman, PhD, *Harvard NeuroDiscovery Center*

Innate Immune Modulatory Strategies for ALS and Alzheimer's Disease

Todd Golde, MD, PhD, *University of Florida*

Development of Small Molecule Hepatocyte Growth Factor Mimetic for the Treatment of Dementia

Joseph Harding, PhD, *M3 Biotechnology*

Allopregnanolone: From Laboratory Discovery to Clinical Trial

Roberta Diaz Brinton, PhD, *University of Southern California*

BACE Inhibition for Alzheimer's Disease: Validation of Target Engagement

Mark Forman, MD, PhD, *Merck & Co., Inc.*

SESSION CHAIR

Marcie Glicksman, PhD, Harvard NeuroDiscovery Center



Dr. Marcie Glicksman is Senior Director, Leads Discovery Group at the Harvard NeuroDiscovery Center's Laboratory for Drug Discovery in Neurodegeneration (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 PhD 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 CEPI 347, a neuroprotective agent directed at a novel kinase, currently in Phase III clinical trials.

Dr. Glicksman 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.

Case Study: From Bench to High Throughput Screen

Marcie Glicksman

Harvard NeuroDiscovery Center, Boston, MA, USA

The Laboratory for Drug Discovery in Neurodegeneration (LDDN) was established in 2001 as a model for how academia can apply its research findings to drug discovery especially in diseases and approaches that are not commonly found in the pharmaceutical industry. Our strategy complements the efforts in industry. The LDDN has an established track record of progressing projects along the drug discovery pathway, from assay development and high-throughput screening through medicinal chemistry on lead compounds and testing candidate drugs in animal models of disease. A specific case study on our project on the glutamate transporter will be presented highlighting the basis for the decision making strategy from assay development through animal studies.

Todd Golde, MD, PhD, University of Florida



Dr. Todd E. Golde is a Professor of Neuroscience at the University of Florida, where he directs the Center for Translational Research in Neurodegenerative Disease. Dr. Golde received his MD/ PhD from Case Western Reserve University. He completed a residency in Laboratory Medicine at University of Pennsylvania. After beginning his independent career at University of Pennsylvania, he moved to Mayo Clinic Florida where he rose from Assistant Professor of Pharmacology to both Professor of Neuroscience and chair of Mayo Clinic's internationally recognized Department of Neuroscience. Dr. Golde has published over 180 peer-reviewed manuscripts which have been cited over 15000 times. Dr. Golde is well known for his translational research in Alzheimer's disease and his work on γ -secretase modulators and immunotherapy for neurodegenerative diseases. His scientific honors include the Paul Beeson Faculty, a Alzheimer's Association Zenith, and MetLife Foundation Awards.

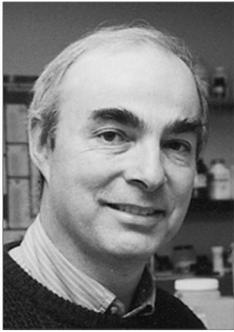
Innate Immune Modulatory Strategies for ALS and Alzheimer's Disease

Todd Golde

University of Florida, Gainesville, FL, USA

Altered central nervous system (CNS) proteostasis characterized by accumulation of extracellular or intracellular proteinaceous deposits is thought to be a key trigger of many neurodegenerative disorders including AD and most forms of ALS. There is considerable evidence that various assemblies of the aggregated proteins that form these inclusions can activate the innate immune system which in turn can contribute to the degenerative cascade. There is also growing evidence that alterations in innate immune signaling can play a key role in regulating proteostasis. We term this complex interplay between the innate immune system and proteinopathy, immunoproteostasis. In a contextually dependent fashion, immunoproteostasis can have positive or negative effects on the proteinopathy and degenerative phenotype. Because of these effects and the plethora of therapeutic targets in the innate immune system, there is considerable interest in manipulating immunoproteostasis for potential disease modification in neurodegenerative diseases. Here we will discuss potential innate immune targets in ALS and AD and provide several unpublished studies that reveal the disease modifying potential of IL-10 in fALS mutant SOD1 mouse models and soluble Toll-like receptors in mouse models of amyloid β deposition. A road-map for further development of these and other innate immune targeting therapies in AD, ALS and other neurodegenerative diseases will be discussed.

Joseph Harding, PhD, M3 Biotechnology



Dr. Harding received his PhD in Chemistry from the University of Delaware in 1974 and did postdoctoral training in the laboratory of Frank Margolis at the Roche Institute of Molecular Biology. He is a professor of physiology and neuroscience at Washington State University where he has been a faculty member since 1976. His long term interest in peptides and peptidomimetics was initially focused on topics in olfaction and the central control of cardiovascular function. More recently his laboratory has turned their attention to the development of small molecule allosteric growth factor regulators as therapeutics for cancer and neurodegenerative disease. This work has spawned two biotechnology companies including M3 Biotechnology, which is developing small molecule hepatocyte growth factor antagonists for the treatment of various cancers and mimetics for the treatment of neurodegenerative diseases including Alzheimer's disease and Parkinson's disease.

Development of Small Molecule Hepatocyte Growth Factor Mimetic for the Treatment of Dementia

Joseph Harding

M3 Biotechnology, Pullman, WA, USA

Enhancement of neurotrophic factor function has long been recognized as a potential treatment option for most neurodegenerative and neurotraumatic disorders. This should be no surprise given the role of neurotrophic factors in the development, maintenance, and repair of the CNS and the need for augmented synaptogenesis, neurogenesis, and neuroprotection in the degenerating nervous system; processes that are under the control of these proteins. The difficulty, of course, is that these growth factor proteins are labile and blood-brain barrier (BBB) impermeable; characteristics that have necessitated the use of complex cell- and viral-based delivery systems that are invasive and costly. Our laboratory has exploited a common feature of many growth factor systems; namely the need to be activated by multimerization. We have intervened at this activation step by constructing small allosteric activators (or antagonists) directed at the multimerization domains. Currently we have been focusing on hepatocyte growth factor (HGF) as a test case because of its role in cancer, fibrosis, regenerative activity, cell survival and the overall potential of HGF-directed drugs as broad-based therapeutics. BBB permeable HGF mimetics, which display powerful synaptogenic activity and are demonstrated to reverse cognitive and motor deficits in several neurodegenerative animal models, are currently being developed as treatment options for dementia and Parkinson's disease.

The desire to determine whether this HGF-directed technology has real clinical potential for the treatment of neurodegenerative diseases including Alzheimer's and Parkinson's motivated us to form M3 Biotechnology, a start-up biopharmaceutical company. M3's current focus is the establishment of M3 as a viable business entity and the advancement of our lead HGF mimetic, MM-201, into human clinical trials for the treatment of neurodegenerative disease. This activity, which is still ongoing, has entailed assembling appropriate business and scientific advisor boards and expertise, the development of relationships with pre-clinical and clinical partners, and raising the of required capital.

Roberta Diaz Brinton, PhD, University of Southern California



Roberta Diaz Brinton, PhD, is the R. Pete Vanderveen Chair in Therapeutic Discovery and Development and Professor of Pharmacology and Pharmaceutical Sciences, Biomedical Engineering and Neurology at the University of Southern California. She directs the Norris Foundation Laboratory for Neuroscience Research, the USC STAR Science Education Program, and Preclinical Translation and Regulatory Services for the SC CTSI. Research in the Brinton laboratory focuses on understanding the mechanisms that lead to Alzheimer's in the aging brain and translating that mechanistic understanding into therapeutics to prevent, delay and treat the disease. Investigative strategies span discovery to translation to clinical science. Translation of discoveries at the bench have resulted in two NIH funded clinical trials for the prevention and treatment of Alzheimer's disease. Dr. Brinton is the PI of the NIH / NIA Program Project on Perimenopause in Brain Aging

and Alzheimer's Disease, the NIA ROI on Estrogen Regulation of Mitochondrial Mechanisms, the NIA UOI on Development of Allopregnanolone as a Neurogenic Regenerative Therapeutic Agent and most recently the NIA Phase Ib clinical trial of Allopregnanolone as Regenerative Therapeutic for MCI & AD. She is CoPI on the NIH / NIA Phase 2 clinical trial of Estrogen Receptor-Beta PhytoSERMs for Management of Menopause and Age-Associated Memory Decline. Dr. Brinton co-founded the biotechnology company, CoCensys and is the joint holder of several patents on therapeutic agents for the treatment of neurological disease. She currently serves on the scientific advisory boards for the Alzheimer's Drug Development Foundation, Alzforum and NIH Board for Scientific Review. Dr. Brinton was named one of the Ten Best Minds by US News and World Report, Woman of the Year by the California State Senate, Science Educator of the Year by the Society for Neuroscience For her decades of commitment to science education to inner city youth of Los Angeles, Dr. Brinton received the Presidential Citizens Medal.

Allopregnanolone: From Laboratory Discovery to Clinical Trial

Roberta Diaz Brinton

University of Southern California, Los Angeles, CA, USA

Regenerative therapeutics hold the promise of self-renewal and repair. While ageing and age-associated neurodegenerative diseases are marked by a decline in self-renewal and repair, a capacity for regeneration is retained. Allopregnanolone, neurosteroid, promotes both the regeneration and repair systems of the brain while simultaneously activity systems that reduce the generation of Alzheimer's pathology. In preclinical analyses in normal aged and transgenic mice for Alzheimer's, allopregnanolone induced the generation and survival of new neurons in the hippocampus and subventricular zone. Allopregnanolone-induced neurogenesis was accompanied by restoration of associative learning and memory function. In the brains of mice with Alzheimer disease, allopregnanolone increased liver X receptor and pregnane X receptor expression, reduced amyloid- β and microglial activation, and increased markers of myelin and white matter generation. Based on a substantial body of preclinical mechanistic and efficacy data, we embarked on a translational development program to advance allopregnanolone to the clinic as a regenerative therapeutic for Alzheimer's disease. Critical to success was a dosing and treatment regimen that was consistent with the temporal requirements of regenerative systems biology of brain. A treatment regimen that adhered to regenerative requirements of brain was also efficacious in reducing Alzheimer's pathology. With an optimized dosing and treatment regimen, analyses of chronic allopregnanolone administration indicated significant neurogenesis, oligodendrogenesis, reduced neuroinflammation and beta-amyloid burden while increasing markers of white matter generation and cholesterol homeostasis. Allopregnanolone meets three of the four drug-like physicochemical properties described by Lipinski's rule that predict the success rate of drugs in development for clinical trials. Pharmacokinetic and pharmacodynamic outcomes, securing GMP material, development of clinically translatable formulations and acquiring regulatory approval will be discussed. Investigation of allopregnanolone as a regenerative therapeutic has provided key insights into mechanistic targets for neurogenesis and disease modification, dosing requirements, optimal treatment regimen, route of administration and the appropriate formulation necessary to advance to proof of concept clinical studies to determine efficacy of allopregnanolone as a regenerative and disease modifying therapeutic for Alzheimer's disease. Outcomes of discovery and translation research led to an NIA funded Phase Ib clinical trial of allopregnanolone in persons with MCI and early Alzheimer's to establish the maximally tolerated dose, safety associated with chronic exposure and establishment of biomarkers of regenerative efficacy. Support for development of allopregnanolone as a regenerative therapeutic for Alzheimer's was provided by Alzheimer's Drug Discovery Foundation and the National Institute on Aging.

Mark Forman, MD, PhD, Merck & Co., Inc.



Mark Forman is currently the Executive Director and Neuroscience Lead in Clinical Pharmacology and Experimental Therapeutics at Merck & Co., Inc.. Dr. Forman joined Merck in 2007 where his work focuses on early clinical drug development, primarily in the therapeutic areas of Neurology, Psychiatry and Oncology.

Prior to joining Merck, Dr. Forman was an Assistant Professor of Pathology at the University of Pennsylvania where his research focused on the pathogenesis of neurodegenerative disease, including Alzheimer's disease, Parkinson's disease and Frontotemporal Dementia. At the University of Pennsylvania, Dr. Forman was Director of the Brain Bank in the Center for Neurodegenerative Disease Research and Director of the Neuropathology Core of the

Alzheimer's Disease Center.

Dr. Forman received his undergraduate education at Yale University with a focus in Molecular Biophysics and Biochemistry. He received his PhD in Immunology at Rockefeller University and his MD at Duke University. Dr. Forman completed residency training in Anatomic Pathology and fellowship training in Neuropathology at the University of Pennsylvania. He also completed postdoctoral training in the Center for Neurodegenerative Disease Research at the University of Pennsylvania with Drs. Virginia Lee and John Trojanowski.

Dr. Forman is the author of more than 70 publications. His work has earned him several awards including the 2003 Experimental Pathologist in Training Award and the 2012 PhRMA Research and Hope Award.

BACE Inhibition for Alzheimer's Disease: Validation of Target Engagement

Mark Forman

Merck & Co., Inc., USA

Compelling evidence implicates the abnormal accumulation of β -amyloid ($A\beta$) peptides in the pathogenesis of Alzheimer's disease. β -secretase (or BACE1) is a membrane bound aspartyl protease that mediates the first step in the generation of $A\beta$ peptides. Thus, inhibition of BACE1 to reduce $A\beta$ production is a promising approach to test the amyloid hypothesis.

Since the cloning of β -secretase over a decade ago, there has been intensive effort to develop BACE1 inhibitors for the treatment of Alzheimer's disease. However, progress has been challenging since BACE1 is associated with intracellular membranes and has an extended, shallow and hydrophilic binding cleft thereby requiring highly permeable and brain penetrant inhibitors. There is also a critical requirement for selectivity relative to other aspartyl proteases (e.g., cathepsin D).

MK-8931 is a potent BACE inhibitor that is highly selective for BACE1 and BACE2 relative to other aspartyl proteases. In preclinical studies, MK-8931 reduces the production of $A\beta$ in the brain and CSF of rodents and primates. The early clinical development program was designed to characterize the safety, pharmacokinetics and pharmacodynamic potential of MK-8931 in healthy volunteers and Alzheimer's disease patients to enable dose selection for subsequent clinical trials that will assess the safety and efficacy of MK-8931 across a broad spectrum of disease severity. In Phase I studies, MK-8931 has been generally well-tolerated in both healthy subjects and Alzheimer's disease patients. The pharmacokinetic profile of MK-8931 is suitable for once daily dosing with good penetration into the central nervous system. The pharmacodynamics of MK-8931 is characterized by a dose-dependent and sustained reduction of CSF $A\beta$ peptides with peak reductions from baseline of up to 94%. Dose-response profiling indicates that 12 mg and 40 mg MK-8931 will inhibit $A\beta$ production by > 50% and > 75%, respectively, in the majority of patients. Thus, MK-8931 presents a unique opportunity to test the amyloid hypothesis of Alzheimer's disease pathogenesis. EPOCH, a Phase 2/3 efficacy trial in mild to moderate Alzheimer's disease was initiated in December 2012.

Funded by Merck and Co., Inc

SESSION V

Developing Science into Products

Chair: Kurt Brunden, PhD, University of Pennsylvania

Session Overview

Novel Approaches to Technology Transfer: Pharma-Academia Collaborations

Robert Zivin, PhD, *University of Miami*

Innovation in Tech Transfer and the Role of the Tech Transfer Office

Todd Huffman, PhD, *The Scripps Research Institute*

A Re-Understanding of How to Protect and Use Intellectual Property

Leslie Meyer-Leon, PhD, JD, *IP Legal Strategies Group PC*

Robert Zivin, PhD, University of Miami



Robert Zivin, PhD, is a Research Associate Professor, Medicine, and Senior Fellow, Wallace H. Coulter Center for Translational Research. His role at the University of Miami is to facilitate the development of new approaches and technologies for improving healthcare. Previously, Dr. Zivin was Senior Director in Johnson & Johnson's Corporate Office of Science & Technology. He has spent 33 years in Healthcare R&D, working in biotechnology, molecular diagnostics and drug discovery. While at J&J, Dr. Zivin worked on the development of new models of collaboration, with the twin aims of facilitating academic partnering and shifting the cost-reward profile of product development.

Dr. Zivin received his PhD from the University of Chicago.

Novel Approaches to Technology Transfer: Pharma-Academia Collaborations

Robert Zivin

University of Miami, Miami, FL, USA

To paraphrase: "The road to products is paved with good IP." Understanding the needs of your commercial partner, creating a shared vision / passion, and outlining a pathway to clinical development are important to success. The presentation will provide insights and suggestions for selling your ideas, as well as a look at some of the possible pitfalls. This understanding is especially critical for advancing concepts to clinical testing in chronic conditions with large and expensive trial designs.

Todd Huffman, PhD, The Scripps Research Institute



Todd Huffman, PhD, is the Head of New Ventures and Director of Drug Discovery Partnerships at the Scripps Research Institute. Todd was previously a founder at S6 Therapeutics, a start-up company developing oncology and metabolic disease therapeutics. Before starting S6, Todd was a venture capitalist at Research Corporation Technologies (RCT) BioVentures where he focused on investments in early stage biotechnology and drug discovery.

Prior to joining RCT, Todd held positions in biomedical licensing at the University of North Carolina at Chapel Hill and the University of Virginia.

Todd earned a PhD in molecular pharmacology from the University of Virginia where he investigated the pathophysiological basis for type II diabetes. Todd is a board member of the University of Virginia School of Medicine's clinical translation initiative for diabetes.

Innovation in Tech Transfer and the Role of the Tech Transfer Office

Todd Huffman

The Scripps Research Institute, La Jolla, CA, USA

The current economic landscape for early stage drug development faces several challenges which threaten to constrain future clinical pipelines and ultimately the creation of novel therapies. Given a tremendous amount of therapeutic unmet need, especially as concerns neurodegenerative diseases, it is vital that we derive new measures to deal with these emergent issues. In this talk, we will examine the structural problems we face and how some of these may be addressed. We will focus on the role that business development/technology transfer offices can play in this ecosystem and the impact that novel business models may provide in fostering more nimble and efficient partnerships with pharmaceutical companies, foundations, and entrepreneurs.

Leslie Meyer-Leon, PhD, JD, IP Legal Strategies Group PC



Leslie Meyer-Leon, a registered patent attorney and founder of IP Legal Strategies Group P.C., represents clients in the biotechnology and pharmaceutical sectors with complex intellectual property matters, and provides consulting services to investors who seek interpretive assistance with Hatch-Waxman and other biotech patent litigation. She has two decades of practical expertise in intellectual property-related opinions and operational planning, transactions and due diligence, in dispute negotiation, and in strategic plans for corporate intellectual property assets. In addition to client practice, Dr. Meyer-Leon has since 2001 served as a Patent Highlights Advisor for Nature Reviews Drug Discovery journal, providing on-going counsel and updates for NRDD's editorial staff on the interpretation of US patent law. Dr. Meyer-Leon is widely recognized in the Boston intellectual property community for her service as President of the Boston Patent Law Association and her 10 years as a member and officer of the BPLA Board of Governors. She now co-chairs the BPLA's Biotechnology Committee. Prior to founding IP Legal Strategies in 2000, Leslie was a patent attorney at Boston law firms including Goodwin Procter, Mintz Levin, and Fish & Richardson. She holds a PhD in Molecular and Cellular Biology from the University of Wisconsin-Madison, and a JD from Boston College Law School.

A Re-Understanding of How to Protect and Use Intellectual Property

Leslie Meyer-Leon

IP Legal Strategies Group PC, Centerville, MA, USA

A strong intellectual property (IP) position remains critical for competitive positioning and risk management at all stages of commercial drug development. But what types of IP can you expect to legally protect, and how can you profit from it? The answer has changed dramatically in recent years, due to revised judicial doctrine, laws, and administrative rules. And as ever, tight IP budgets make it critical to do more with less. During this talk we will reassess what IP is protectable and worth protecting, and how to use it to competitive advantage, under today's altered IP landscape.

SESSION VI

What do Partners Look For? A Perspective from Pharma, Private Investors and Philanthropy

Chair: Frank Longo, MD, PhD, Stanford University and Pharmatropix

Introduction: Challenges in Securing Partnerships

Frank Longo, MD, PhD, *Stanford University and Pharmatropix*

Panel Discussion: What do Partners Look For?

Panelists:

Adrian Howd, PhD, *Evotec AG*

Sanjeev Munshi, PhD, *Merck & Co., Inc.*

Dennis Yamashita, PhD, *GlaxoSmithKline*

Marco Baptista, PhD, *Michael J. Fox Foundation for Parkinson's Research*

SESSION CHAIR

Frank Longo, MD, PhD, Stanford University and PharmatropiX



Dr. Longo is Professor and Chairman, Department of Neurology and Neurological Sciences at Stanford University. He received his MD in 1981 and PhD in Neurosciences in 1983 from UC San Diego. He completed his neurology and fellowship training in the Department of Neurology at UC San Francisco where he was then recruited as an assistant professor and promoted to professor and vice chair. From 2001 to 2005 he was chair of the Department of Neurology at the University of North Carolina-Chapel Hill and since 2006 has served as chair of the Department of Neurology and Neurological Sciences at Stanford. With support from the Alzheimer's Drug Discovery Foundation, Alzheimer's Association, and the NIH, he and his team have pioneered small molecule treatment strategies for Alzheimer's and other neurodegenerative diseases. In 2005, while at UNC, he founded PharmatropiX, a company

focused on the commercial development of these therapies. A lead candidate compound for Alzheimer's disease has begun phase I human trials.

Challenges in Securing Partnerships

Frank Longo

Stanford University and PharmatropiX, Stanford, CA, USA

Drug discovery and early stage development programs generally share the common goal of securing funding partners and a pharma partner at the appropriate stages of drug development. From the very first steps, it is important to have an understanding of the profiles and specific features that are sought by these partners. Funders will want to know about specific milestones that will promote or allow pharma engagement and the time frames, risks and costs involved. Pharma due diligence will focus on many key issues including: IP, evidence for target/mechanism importance, evidence for target/mechanism engagement, potential side effects, relevance and availability of biomarkers, competitive landscape, etc. Being well versed up front regarding mechanisms by which partners evaluate technologies is a key requirement for effective early stage strategization.

Adrian Howd, PhD, Evotec AG



Adrian Howd is currently EVP, Head of Neuroscience & Corporate Development at Evotec AG. His role brings overall responsibility for the management, development and growth of the current CNS portfolio and for new drug discovery opportunities in this therapeutic area. He also leads the process for corporate development and corporate positioning activities at Evotec.

Dr. Howd has over 20 years of experience in biotechnology, from both academic research and investment banking perspectives. Adrian has a PhD in Molecular Neuroscience from the University of London and was awarded a visiting postdoctoral research fellowship at the NIH in Bethesda, MD. He has also studied and undertaken research at the Institute of Psychiatry, King's College London. He is a Board member and Trustee of the Multiple Sclerosis Society in and also serves as a member of the Society's Research Strategy and Finance Committees. In the financial sector, Dr. Howd has held both sell-side and buy-side roles, being a highly ranked sell side analyst at Berenberg, Nomura and ABN Amro where he was Global Head of Healthcare Research. He also gained buy-side experience running a Healthcare portfolio as part of the Principal Strategies Group at ABN Amro. Dr. Howd has broad experience of equity capital markets, including IPOs, fundraisings, privatisations and M&A transactions.

Sanjeev Munshi, PhD, Merck & Co., Inc



Sanjeev Munshi is a Director in the Business Development and Licensing organization of the Merck Research Laboratories (BD&L-MRL). Dr. Munshi's role is to identify partnering opportunities that fit with Merck's strategic research and development goals across all therapeutic and technology areas. Sanjeev is primarily responsible for scouting and managing alliances in the Southeastern US.

Dr. Munshi graduated from Kashmir University, India, with a BS in chemistry and physics. He earned his PhD in molecular biophysics (Structural Biology) from Indian Institute of Science, India, and MBA from Villanova University. Following a postdoctoral fellowship in structural virology at Purdue University and a brief stint at National Cancer Institute, he joined the Merck Research Labs in West Point, PA in 1995. Prior to joining the BD&L-MRL group in 2010, Dr. Munshi headed the Structural Biology department at Merck.

Dennis Yamashita, PhD, GlaxoSmithKline



Dr. Dennis Yamashita is currently an Entrepreneur in Residence and Executive Director in Discovery Partnerships with Academia (DPAc) at GlaxoSmithKline (GSK), Boston. From 2008 to 2013, Dr. Yamashita was VP and Head of Chemistry at Trevena, a start-up biotech company focused on the identification of GPCR biased ligands. While at Trevena, he led teams resulting in the discovery of TRV027, an AT1R beta-arrestin biased ligand that has completed Ph 2a clinical trials for the treatment of acute heart failure. His group also discovered TRV130, a Mu opioid receptor G-biased ligand that has completed Ph 1a clinical trials that is being developed for a post-surgical pain indication and TRV734, a Mu opioid receptor G-biased ligand that is being developed to treat severe acute and chronic pain.

Prior to working at Trevena, Dr. Yamashita was a medicinal chemist at GlaxoSmithKline and SmithKline Beecham from 1991-2008 in which he worked in the fields of oncology, osteoporosis, osteoarthritis, endocrinology, immunology, inflammation, and asthma.

Dr. Yamashita received his PhD in Organic Chemistry at Yale University under the supervision of Samuel J. Danishefsky and his BS in Chemistry at MIT.

Marco Baptista, PhD, The Michael J. Fox Foundation for Parkinson's Research



Dr. Baptista earned an undergraduate degree in Psychology from the University of Toronto and a PhD in Neuroscience from McMaster University, Canada. After completing his postdoctoral research at The Scripps Research Institute in La Jolla, Dr. Baptista spent over five years in the pharmaceutical industry leading a preclinical Parkinson's program.

He has been at The Michael J. Fox Foundation for Parkinson's Research since 2012, helping drive the funding of translational research.

NOTES

NOTES

15TH INTERNATIONAL CONFERENCE ON ALZHEIMER'S DRUG DISCOVERY

September 8-9, 2014 • Jersey City, NJ (across the Hudson River from NYC)

Presented by the Alzheimer's Drug Discovery Foundation

GENERAL INFORMATION

This annual conference brings together academic and industry scientists intent on accelerating the development of innovative treatments for Alzheimer's disease and related dementias. The ADDF's funded investigators and top level scientists in the field will present their current research, provide progress updates and stimulate discussion. The conference offers ample opportunities for collaboration and partnering.

OBJECTIVES

- Highlight scientific progress on drug discovery programs aimed at treating Alzheimer's disease and related dementias.
- Increase networking opportunities for scientists to share information and resources.
- Foster interdisciplinary and public-private partnerships and alliances.

SCHOLARSHIPS

The Alzheimer's Drug Discovery Foundation invites applications for the **2014 ADDF Young Investigator Scholarships**. These prestigious Scholarships recognize early achievements and seek to encourage the career development of the next generation of research scientists.

TARGET AUDIENCE

The conference generally attracts 150 attendees from around the globe. Attendees include:

- Academic and industry scientists engaged in drug discovery research for Alzheimer's disease
- Business development and licensing professionals
- Alliance management professionals
- Venture capitalists and other investors



Alzheimer's
Drug Discovery
Foundation

SINGLE REGISTRATION (all fees in US Dollars)	EARLY BIRD (Received by Aug 8, 2014)	STANDARD (Received after Aug 8, 2014)	AT DOOR
Post-Doctoral/Graduate Student*	\$225	\$300	\$375
Academia/Government/Non-Profits/ Start-up Biotechnology Company**	\$300	\$375	\$425
Industry and Private Practice	\$550	\$650	\$700
Networking Reception Guest***	\$35	\$35	\$35

www.alzdiscovery.org

* Proof of academic status is required

** A Start-up Biotechnology Company is defined as an organization less than three years old and with 20 or fewer employees.

*** Guest access to the reception only (guest must be accompanied by the registrant).

Discounts are offered for groups of three or more from the same organizations. Press passes are also available. For details, please contact the conference secretariat.



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