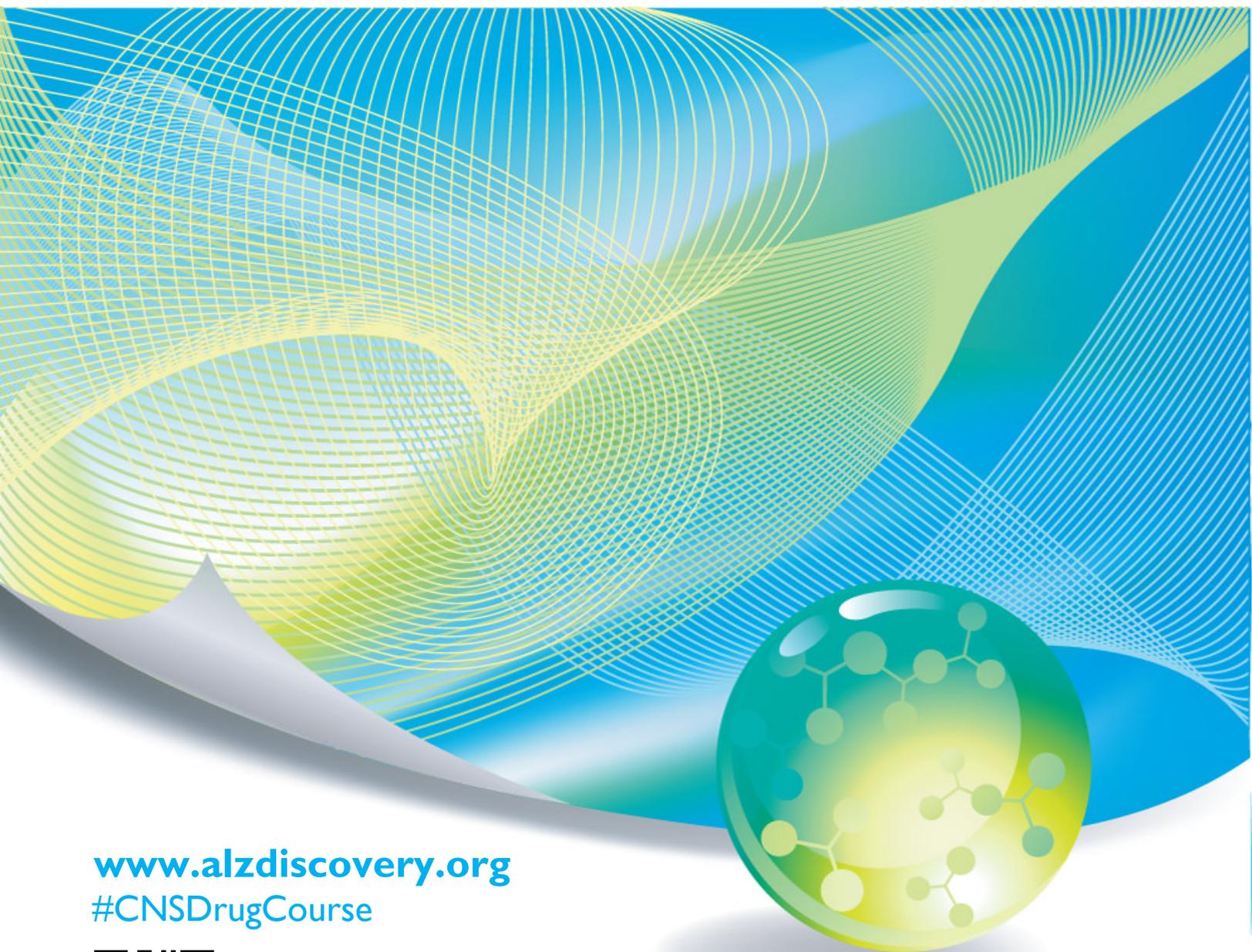


# 9<sup>th</sup> ANNUAL DRUG DISCOVERY FOR NEURODEGENERATION CONFERENCE: An Intensive Course on Translating Research into Drugs

March 1-3, 2015 • San Diego, CA

*Presented by the Alzheimer's Drug Discovery Foundation*



[www.alzdiscovery.org](http://www.alzdiscovery.org)  
#CNSDrugCourse



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# LIST OF ABBREVIATIONS

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- **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
- **FIH**-First-in-humans
- **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
- **MOA**- Mechanism of action
- **MTD**-Maximum tolerated or minimally toxic dose
- **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
- **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<sub>max</sub>** = maximum plasma concentration
  - **T<sub>max</sub>** = time to achieve maximum plasma concentration
  - **T<sub>1/2</sub>** = elimination half-life
  - **F** = percent bioavailability
- **TPP**-Target product profile

# ALZHEIMER'S DRUG DISCOVERY FOUNDATION

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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 **\$75 million to fund nearly 500 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 \$2 billion in follow-on funding from the government, pharmaceutical companies and venture capital firms.
3. The Alzheimer's Drug Discovery Foundation (ADDF) has partnered with OnDeckBiotech to improve and expand the ADDF ACCESS program, which gives 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 central nervous system diseases. The platform enables users to easily distribute requests for proposals to multiple vendors, execute confidentiality agreements securely, and manage projects and communications with companies. ADDF ACCESS additionally provides educational resources on the drug discovery process and guidance on CRO selection and management.

Register for free at <http://addfaccess.ondeckbiotech.com>.

# ADDF ANNUAL CONFERENCES

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

Our annual *International Conference for Alzheimer's 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 spring, 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

---

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

**Julie Frearson, PhD**, Executive Director, Scientific Alliances Early Discovery, Charles River Laboratories

**Marcie Glicksman, PhD**, Vice President Biology, Orig3n, Inc.

**Frank Longo, MD, PhD**, Professor and Chair Department of Neurology and Neurological Sciences, Stanford University

**Suzana Petanceska, PhD**, Program Director, National Institute on Aging

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

**Edward Spack, PhD**, Managing Director, Fast Forward LLC

**D. Martin Watterson, PhD**, Professor, Molecular Pharmacology & Biology Chemistry, Northwestern University; Director, Drug Discovery Program

## CONFERENCE DELIVERABLES

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A webcast of the entire conference will be made available on the Alzheimer's Drug Discovery Foundation website ([www.alzdiscovery.org](http://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 9<sup>th</sup> *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.

This year, we are pleased to host the meeting in San Diego, CA, home to 21 Nobel Laureates in the sciences. The life sciences industry in San Diego began to emerge in the 1980s, and by the turn of the century, it became one of the most dense life science clusters in the country. San Diego is home to more than 700 life science, bio-medical companies, more than 80 world-renowned research institutions, 140 contract research organizations (CROs), and along with its close proximity to La Jolla and Sorrento Valley, it makes San Diego a hub to fuel innovative research. We are thrilled to be able to participate in this community and bring our conference to this progressive state.

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.

Our meeting is made possible by the generous support of our sponsors: Eli Lilly & Company, Merck, Forest Laboratories Inc., National Multiple Sclerosis Society, Taub Institute for Research on Alzheimer's Disease and the Aging Brain, PsychoGenics, IRBM and our exhibitors: IDSC, SAGE Labs, Taconic, Pharmatek, Valley Biosystems, Bachem, InterVivo Solutions, QPS, Brains Online, Gene Tools LLC, and OnDeckBiotech. 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  
*Founding Executive Director*  
*Chief Science Officer*  
Alzheimer's Drug Discovery Foundation

**9<sup>th</sup> ANNUAL DRUG DISCOVERY FOR NEURODEGENERATION CONFERENCE:  
AN INTENSIVE COURSE ON TRANSLATING RESEARCH INTO DRUGS  
PROGRAM**

**Sunday, March 1, 2015**

2:00pm–4:00	Registration — <i>Foyer (2nd Floor)</i>
4:00–4:20	<b>Welcome &amp; Opening Remarks: Challenges and Opportunities in Academic Drug Discovery</b> <b>Howard Fillit, MD</b> — Alzheimer's Drug Discovery Foundation
4:20–5:05	<b>KEYNOTE: A Systems Biology Approach to Understanding Neurodegenerative Disease</b> <b>Leroy Hood, MD, PhD</b> — Institute for Systems Biology
5:05–5:15	Q&A
5:15–7:00	Welcoming Reception — <i>Riviera Terrace (3rd Floor)</i>

**Monday, March 2, 2015**

7:00am–7:00pm	Registration — <i>Foyer (2nd Floor)</i>
7:30am–8:30	Continental Breakfast — <i>Fontainebleau Room (2nd Floor)</i>
8:30–8:35	<b>Welcome &amp; Opening Remarks</b> <b>Howard Fillit, MD</b> — Alzheimer's Drug Discovery Foundation
8:35–8:50	<b>Preclinical Therapeutics Development for Neurological Disorders: Funding and Resources</b> <b>Lorenzo Refolo, PhD</b> — National Institute on Aging
8:50–9:05	<b>NINDS Opportunities for Translational Research Funding</b> <b>Mary Ann Pellemounter, PhD</b> — National Institute of Neurological Disorders and Stroke

**I. Embarking on a Drug Discovery Campaign**

**Chair: Julie Frearson, PhD — Charles River Laboratories**

9:05–9:10	<b>Session Overview</b> <b>Julie Frearson, PhD</b> — Charles River Laboratories
9:10–9:30	<b>Assembling the Right Interdisciplinary Team from the Beginning</b> <b>Julie Frearson, PhD</b> — Charles River Laboratories
9:30–9:40	Q&A
9:40–10:00	<b>Improving Clinical Success through Translational Science for Optimal Target Validation and Biomarkers</b> <b>Kalpna Merchant, PhD</b> — TransThera Consulting Co.
10:00–10:10	Q&A
10:10–10:30	<b>Considerations and Limitations for Assay Development</b> <b>William Janzen</b> — Epizyme, Inc.
10:30–10:40	Q&A
10:40–11:00	Exhibitor Session and Break

**II. Hit Selection and Lead Optimization**

**Chair: D. Martin Watterson, PhD — Northwestern University**

11:00–11:05	<b>Session Overview</b> <b>D. Martin Watterson, PhD</b> — Northwestern University
11:05–11:25	<b>From HTS through Hit Identification and Evaluation: Considerations and Best Practices</b> <b>Thomas Chung, PhD</b> — Sanford-Burnham Medical Research Institute
11:25–11:35	Q&A
11:35–11:55	<b>Learning from Precedents: Project Flow in Early Stage Small Molecule Refinement for CNS Drug Discovery</b> <b>D. Martin Watterson, PhD</b> — Northwestern University
11:55–12:05 pm	Q&A
12:05–12:25	<b>PK/PD in Preclinical Development</b> <b>Barry Greenberg, PhD</b> — University Health Network
12:25–12:35	Q&A
12:35–1:40	Lunch and Poster Session — <i>Fontainebleau Room (2nd Floor)</i> <i>All Poster Presenters Should Stand by their Posters from 1:05 to 1:40pm</i>

**III. Drug Discovery: From Lead to Clinical Candidate**

**Chair: Edward Spack, PhD—Fast Forward, LLC**

1:40–1:45	<b>Session Overview</b> <b>Edward Spack, PhD</b> — Fast Forward, LLC
1:45–2:05	<b>Lead to Clinical Candidate: Essential Chemical Development Practices</b> <b>Bruce Molino, PhD</b> — Albany Molecular Research Inc. (AMRI)
2:05–2:15	Q&A
2:15–2:35	<b>Early Phase Drug Product Strategies: What Formulation Strategy is Best for Your Goals?</b> <b>Bryan Knox</b> — Pharmatek
2:35–2:45	Q&A
2:45–3:05	<b>Requirements for an IND and Early Considerations</b> <b>Edward Spack, PhD</b> — Fast Forward, LLC

3:05–3:15	Q&A
3:15–3:55	Exhibitor Session and Break
3:55–4:15	<b>Virtual R&amp;D Operations - How to work with CROs and Consultants</b> <b>Tilmann Brotz, PhD</b> — Achaogen, Inc.
4:15–4:25	Q&A
4:25–4:40	<b>ADDF ACCESS &amp; Young Investigator Scholarship Awards Presentation and Closing Remarks</b> <b>Lauren Friedman, PhD</b> — Alzheimer's Drug Discovery Foundation
4:40–6:00	<b>Partnering Session</b> — <i>Riviera Room (3rd Floor)</i>
4:40–7:00	Networking Reception — <i>Riviera Terrace (3rd Floor)</i>

## Tuesday, March 3, 2015

7:30am–8:15	<b>Partnering Session</b> — <i>Riviera Room (3rd Floor)</i>
7:30–8:30	Continental Breakfast — <i>Fontainebleau Room (2nd Floor)</i>
8:30–8:35	<b>Welcome &amp; Opening Remarks</b> <b>Diana Shineman, PhD</b> — Alzheimer's Drug Discovery Foundation
8:35–9:05	<b>KEYNOTE: Utilizing hiPSC-derived Differentiated Cells for High-throughput Drug Screening</b> <b>Anne Bang, PhD</b> — Sanford-Burnham Medical Research Institute
9:05–9:15	Q&A

### IV. Strategies for CNS Targets – Case Study Examples

**Chair: Marcie Glicksman, PhD— Orig3n, Inc.**

9:15–9:20	<b>Session Overview</b> <b>Marcie Glicksman, PhD</b> — Orig3n, Inc.
9:20–9:40	<b>Case Study: The Identification of Klotho Enhancers</b> <b>Marcie Glicksman, PhD</b> — Orig3n, Inc.
9:40–9:50	Q&A
9:50–10:10	<b>CP2: Generating New Intellectual Property</b> <b>Eugenia Trushina, PhD</b> — Mayo Clinic
10:10–10:20	Q&A
10:20–10:40	<b>Meeting Regulatory and Commercialization Challenges in Advancing Agb101 to Slow Progression in Amnesic Mild Cognitive Impairment Due to Alzheimer's Disease</b> <b>Michela Gallagher, PhD</b> — AgeneBio, Inc.
10:40–10:50	Q&A
10:50–11:10	Exhibitor Session and Break
11:10–11:30	<b>Generating Proof of Concept for AD Using an Orphan Indication</b> <b>Brandon Wustman, PhD</b> — Orphi Therapeutics
11:30–11:40	Q&A
11:40–12:00 pm	<b>Allopregnanolone: From Laboratory Discovery to Clinical Trial</b> <b>Roberta Diaz Brinton, PhD</b> — University of Southern California
12:00–12:10	Q&A
12:10–1:10	Lunch and Poster Session — <i>Fontainebleau Room (2nd Floor)</i> <i>All Poster Presenters Should Stand by their Posters from 12:40 to 1:10 pm</i>

### V. Developing Science into Products

**Chair: Frank Longo, MD, PhD — Stanford University and Pharmatrophix**

1:10–1:15	<b>Session Overview</b> <b>Frank Longo, MD, PhD</b> — Stanford University and Pharmatrophix
1:15–1:35	<b>Models for Technology Translation: Innovative Incubator Models</b> <b>Guy Seabrook, PhD</b> — Johnson & Johnson Innovation
1:35–1:45	Q&A
1:45–2:05	<b>Intellectual Property Strategies: What and When to File for Patent Protection</b> <b>Leslie Meyer-Leon, PhD, JD</b> — IP Legal Strategies Group PC
2:05–2:15	Q&A
2:15–2:35	<b>A New Paradigm for Translational Research</b> <b>James Schaeffer, PhD</b> — California Institute for Biomedical Research (Calibr)
2:35–2:45	Q&A
2:45–3:05	Exhibitor Session and Break
3:05–3:15	<b>Developing a Biotechnology Company Out of Academia</b> <b>Frank Longo, MD, PhD</b> — Stanford University & Pharmatrophix
3:15–4:00	<b>Panel Discussion: Novel Opportunities for Identifying a Development Partner</b> <b>Mark Allegretta, PhD</b> — National Multiple Sclerosis Society <b>Michela Gallagher, PhD</b> — AgeneBio <b>Leslie Meyer-Leon, PhD, JD</b> — IP Legal Strategies Group PC <b>James Schaeffer, PhD</b> — California Institute for Biomedical Research (Calibr) <b>Guy Seabrook, PhD</b> — Johnson & Johnson Innovation
4:00–4:15pm	<b>Closing Remarks</b> <b>Howard Fillit, MD</b> — Alzheimer's Drug Discovery Foundation



**National  
Multiple Sclerosis  
Society**

# FUNDING OPPORTUNITIES IN MS RESEARCH

**WE NEED YOU!** To achieve our vision of a world free of MS, the National MS Society supports a wide variety of research and training programs aimed at stopping MS in its tracks, restoring function, and ending the disease forever.

## AREAS OF RESEARCH EMPHASIS INCLUDE:

- Understanding and preventing MS progression
- CNS repair/neuroprotection
- Lifestyle/wellness factors
- Patient management, care and rehabilitation
- Immunologic basis of MS
- Pathology/Pathogenesis of MS
- Genetics and gender differences
- Infectious triggers and risk factors
- Cognitive and psychosocial issues
- Clinical trials, Preclinical testing
- Health care delivery and policy
- Measures of disease activity, diagnostics, imaging, surrogate and biomarkers

## VISIT OUR WEBSITE FOR DETAILS AND DEADLINES

[www.nationalMSSociety.org/ResearchFunding](http://www.nationalMSSociety.org/ResearchFunding)



STOPPING THE DISEASE



RESTORING WHAT'S BEEN LOST



ENDING MS FOREVER

## QUESTIONS?

Research funding opportunities: [MSResearch@nmss.org](mailto:MSResearch@nmss.org) or

Commercial research funding opportunities: [Research@FastForward.org](mailto:Research@FastForward.org)

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# 2015 ADDF AWARDS and SCHOLARSHIPS

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Congratulations to all of the 2015 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.

## 2015 ADDF OUTSTANDING YOUNG INVESTIGATOR AWARDS

**Anne-Sophie Cornec, PhD** — University of Pennsylvania

**Mark Halliday, PhD** — Medical Research Council

**Christopher Holler, PhD** — Emory University

**Abhijit Kulkarni, MS** — Northeastern University

**Christine Solinsky, MS** — University of Southern California

## 2015 ADDF YOUNG INVESTIGATOR SCHOLARSHIPS

**Pavithra Chandramowliswaran** — Georgia Institute of Technology

**Drew DeBay, PhD (cand.)** — Dalhousie University

**Yevgeny Aster Dulla, BS** — Kumamoto University Grad. School of Pharmaceutical Sciences

**Martin Estrada, PhD (cand.)** — Medicinal Chemistry Institute - CSIC

**Laura Haas, PhD (cand.)** — Yale University

**Jane Hettinger, BS** — Washington University, St Louis

**Holly Hunsberger, MS** — West Virginia University

**Lisa Kirouac, PhD (cand.)** — University of South Florida Health Byrd Alzheimer's Institute

**Zhen Lu, PhD** — University of Wyoming

**Maryam Masood, MS** — National University of Science and Technology

**Poonam Meena, PhD (cand.)** — Dr. B.R Ambedkar Centre for Biomedical Research

**Loqman Mohamed, PhD (cand.)** — University of Louisiana, Monroe

**Eduardo Luiz Moreira, PhD** — Centro de Inovação e Ensaios Preclínicos

**Ana Pereira, MD** — Rockefeller University

**Atish Prakash, PhD** — Universiti Teknologi Mara (UiTM)

**Arti Singh, PhD** — Punjab University

**Koreswara Rao Valasani, PhD** — The University of Kansas

**Rik van der Kant, PhD** — University of California, San Diego

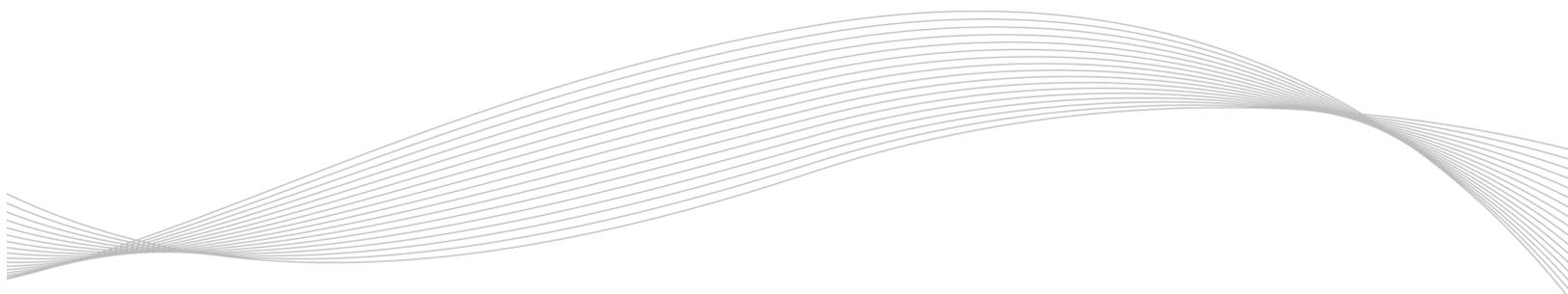
**Changning Wang, PhD** — Massachusetts General Hospital/Harvard Medical School

**Thomas Williams, PhD** — Case Western Reserve University

**Lynda Wilmott, PhD** — University of Tennessee Health Science Center

**Bitna Yi, PhD** — Stanford University

# **CHAIRS AND SPEAKERS**



# **BIOS AND ABSTRACTS**

## DAY I: Welcome Notes

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### 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.

## DAY I: Keynote Lecture

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### Leroy Hood, MD, PhD, Institute for Systems Biology



Leroy Hood, MD, PhD, has focused his research on the study of molecular immunology, biotechnology, genomics and systems biology. His professional career began at Caltech where he and his colleagues pioneered four instruments—the DNA gene sequencer and synthesizer, and the protein synthesizer and sequencer—which comprise the technological foundation for contemporary molecular biology. In particular, the DNA sequencer has revolutionized genomics by allowing the rapid automated sequencing of DNA, which played a crucial role in contributing to the successful mapping of the human genome during the 1990s. His studies on antibody diversity transformed our understanding of the mechanisms for producing antibody diversity. In 1992, Dr. Hood moved to the University of Washington as founder and Chairman of the first cross-disciplinary department in biology—the Department of Molecular Biotechnology. In 2000, he co-founded the first Institute for Systems Biology in Seattle, WA to pioneer systems approaches to biology and medicine. It was during this time that he began his systems-driven studies on disease and focused on neurodegeneration and cancer.

Dr. Hood was awarded the Lasker Prize for studies of immune diversity in 1987 and the 2002 Koyoto Prize for developing advanced technologies. He received the 2003 Lemelson–MIT Prize for Innovation and Invention and at that time was awarded the 2003 Association for Molecular Pathology (AMP) Award for Excellence in Molecular Diagnostics and the 2004 Biotechnology Heritage Award for lifetime achievements in biotechnology. His lifelong contributions to biotechnology have earned him the 2006 Heinz Award in Technology, the Economy and Employment for his extraordinary breakthroughs in biomedical science at the genetic level. He was elected to the Inventors Hall of Fame for the automated DNA sequencer in 2007. In 2011 he received the NAE's Russ Prize for developing the automated DNA sequencer that revolutionized genomics and medicine. In 2013 he received the National Medal of Science from President Obama.

In 2015, Dr. Hood was chosen as one of the world's 50 most influential scientists. He has published more than 750 peer-reviewed papers, received 36 patents, and has coauthored textbooks in biochemistry, immunology, molecular biology, and genetics and is just finishing a text on systems biology. Dr. Hood is a member of the National Academy of Sciences, the American Philosophical Society, the American Association of Arts and Sciences, the Institute of Medicine and the National Academy of Engineering. He is one of 10 (of more than 6,000 members) scientists elected to all three academies (NAS, NAE and IOM). Dr. Hood has also played a role in founding more than 15 biotechnology companies, including Amgen, Applied Biosystems, Systemix, Darwin, Rosetta, and the newly formed diagnostic company, Integrated Diagnostics. He has received 17 honorary degrees from national and international institutions. He is currently pioneering systems medicine and the systems approach to disease with the ultimate object of transforming healthcare to a discipline that is predictive, preventive, personalized and participatory.

---

### A Systems Biology Approach to Understanding Neurodegenerative Disease

Leroy Hood

*Institute for Systems Biology, Seattle, WA, USA*

Systems medicine is the application of systems-biology approaches to disease. I will focus on several new opportunities that emerge from systems medicine and illustrate how these transform how we approach disease and healthcare. These include dynamical studies of disease-perturbed biological networks, the complete genome sequence analyses of families to identify disease genes, and a systems-approach to blood diagnostics. Systems medicine has reached a tipping point and is already beginning to transform the practice of medicine. Three converging opportunities—systems medicine, big data (and its analytics) and patient-activated social networks—are leading to a proactive medicine that is predictive, personalized, preventive and participatory (P4). I will contrast P4 medicine with contemporary evidence-based medicine and discuss its societal implications for healthcare. I will discuss how we plan to introduce P4 medicine into the current healthcare system with a P4 pilot program—a longitudinal, digital-age study on 100,000 well patients. We are already 10 months into a study of 105 well individual and the preliminary results from these studies are striking. This approach can be used to study any disease—and I will give several illustrations including Alzheimer's disease. These advances will have profound implications for healthcare and society.

## DAY 2: Preclinical Therapeutics Development for Neurological Disorders: Funding and Resources

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### **Lorenzo Refolo, PhD, National Institute on Aging**



Lorenzo Refolo, PhD, 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.

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## **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.

## Mary Ann Pellemounter, PhD, National Institute for Neurological Diseases and Stroke



Mary Ann Pellemounter, PhD, is a Scientific Project Manager in the Office of Translational Research at the National Institute for Neurological Diseases and Stroke.

She has over 25 years of experience in scientific research and over 20 years of experience in drug discovery and development. She conducted drug discovery research in preclinical pharmacology at Abbot, Amgen and Neurocrine Biosciences. During her tenure at Amgen, she and her group characterized the neuropharmacological, metabolic and behavioral effects of BDNF, GDNF, leptin, MC4R agonists, AGRP and NPY receptor modulators, resulting in the progression of leptin into clinical testing.

Dr. Pellemounter led in vivo pharmacology research at Neurocrine Biosciences in the areas of neuropsychiatry, sleep, cognition and obesity. She was the Director of Obesity Research at Bristol Myers Squibb for over 10 years, where she led a group of 32 scientists in the discovery and development of therapeutics to treat metabolic disease and its complications, resulting in the progression of multiple preclinical assets into clinical development. She has more than 60 published original research articles, reviews and book chapters, is the author of multiple published patents relating to the discovery and use of leptin and has received numerous research grants and awards in the fields of cognition, aging and neuropsychiatry.

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## NINDS Opportunities for Translational Research Funding

Mary Ann Pellemounter

*National Institute for Neurological Diseases and Stroke, Bethesda, MD, USA*

The Office of Translational Research (OTR) resides within the National Institute of Neurological Disorders and Stroke (NINDS), which is one of the Institutes of the National Institutes of Health (NIH). The mission of the OTR is to accelerate the preclinical discovery and development of new therapeutic interventions for neurological disorders. The OTR offers a variety of programs that support the design, implementation, and management of research activities focused on the discovery and development of therapeutics consistent with the mission of the OTR. The programs include:

- 1) Innovation Grants to Nurture Initial Translational Efforts (IGNITE),
- 2) Blueprint Neurotherapeutics Network (BPN),
- 3) Cooperative Research to Enable and Advance Translational Enterprises (CREATE),
- 4) The Anticonvulsant Screening Program (ASP),
- 5) The Small Business Innovative Research Program (SBIR) and
- 6) Countermeasures Against Chemical Threats (CounterACT).

These programs offer funding mechanisms that support the drug discovery and development process, from the exploratory stage through early development. Since the overall goal of these translational funding programs is to advance successful therapeutics to approval for use in humans, a significant focus of the OTR is to help grantees position their therapeutic assets for continued (advanced-stage) development through partnership and licensing strategies. We will provide overviews on several of the programs listed above, including the intellectual property and financial frameworks, and how their processes can link to successful development outcomes.

## **SESSION I**

### **Embarking on a Drug Discovery Campaign**

**Chair: Julie Frearson, PhD** — Charles River Laboratories

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#### **Session Overview**

##### **Assembling the Right Interdisciplinary Team from the Beginning**

Julie Frearson, PhD — Charles River Laboratories

##### **Improving Clinical Success through Translational Science for Optimal Target Validation and Biomarkers**

Kalpana Merchant, PhD — TransThera Consulting Co.

##### **Considerations and Limitations for Assay Development**

William Janzen — Epizyme, Inc.

# SESSION I: Embarking on a Drug Discovery Campaign

## CHAIR

**Julie Frearson, PhD**, Charles River Laboratories

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Julie Frearson, PhD, studied signal transduction in vascular endothelial cells while working on her doctorate 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, Julie joined BioFocus (now Charles River) in 2011 in a Scientific Alliances role. She now leads the Early Discovery groups' venture into new partnerships with the non-profit sector, including academic institutions and patient foundations in USA.

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## Assembling the Right Interdisciplinary Team from the Beginning

Julie Frearson

*Charles River Laboratories, Wilmington, MA, 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 nomination of a candidate for non-clinical development. 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 I: Embarking on a Drug Discovery Campaign

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### **Kalpana Merchant, PhD, TransThera Consulting Co**



Kalpana Merchant, PhD, has established a life sciences business that provides consultancy services for drug discovery and development and associated enabling technologies. In this capacity, she is an Advisor to the Michael J Fox Foundation for Parkinson's Research and a member of their Executive Scientific Advisory Board. She consults for serves on the Scientific Advisory Boards for Lysosomal Therapeutics, Inc., and Siragen Pharmaceuticals, LLC. She also is an advisor to Third Rock Ventures and other life sciences venture and start-up companies.

Prior to establishing TransThera Consulting Co, Kalpana worked in the US pharmaceutical industry in drug discovery research for nearly 21 years as an individual contributor and in leadership and management roles. Most recently she was at Eli Lilly and Company as the Chief Scientific Officer for Tailored Therapeutics where she was accountable for scientific and business strategies to deliver tailored therapies with associated biomarkers and companion diagnostics for the neuroscience portfolio – from discovery through Phase III. The neuroscience tailoring strategy leveraged the infrastructure of expertise, technologies, and approaches she established as the Chief Scientific Officer of Translational Science, which supported neuroscience, oncology, metabolic disorders and musculoskeletal therapeutic areas at Eli Lilly.

Kalpana received her PhD in neuropharmacology from the University of Utah. Following a postdoctoral research fellowship at University of Washington, she was appointed as an Assistant Professor of Psychiatry at the same institution. She was recruited to Lilly in 2003 from a position of Senior Research Advisor and Fellow at Pharmacia Corp., where she had contributed to neuroscience drug discovery research for about 10 years. Kalpana is engaged in the wider scientific community via her service on NIH Study Sections, 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.

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### **Improving Clinical Success through Translational Science for Optimal Target Validation and Biomarkers**

Kalpana Merchant

*TransThera Consulting Co, Zionsville, IN, USA*

Addressing unmet medical needs for CNS disorders, and particularly chronic neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, remains one of the greatest opportunities. However, there are significant challenges that have hampered the field and led to several high profile phase 3 failures. This talk will focus on translational science approaches to improve the success rate of CNS drugs through optimal target validation and biomarkers. Specifically, translational approaches to establish the relevancy of a drug target or target pathway to disease biology using patient-derived multi-dimensional information, from human genetics to pathway knowledge and pharmacology, will be discussed. Secondly, the talk will highlight the need for robust biomarkers for drug development programs by demonstrating their importance for the selection of clinical doses/dosing regimens, establishing initial proof of efficacy, stratification of patients and ultimately to develop surrogate end-points. Specific examples will be given for biomarker applications outlined above to demonstrate their utility in drug discovery and development. The overall unifying concept of the talk is to highlight the importance of founding therapeutic development programs on deep understanding of disease biology in individual patient populations.

## SESSION I: Embarking on a Drug Discovery Campaign

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### William Janzen, Epizyme, Inc.



William Janzen is the Executive Director of Lead Discovery at Epizyme, Inc.

Mr. Janzen has over twenty years of experience in innovative drug discovery and has been a leader in high throughput screening for lead generation in academics, start-up companies and large pharmaceutical ventures.

He has held executive and operational positions in the pharmaceutical industry including President and Chief Operating Officer of Amphora Discovery and Director of Lead Generation Technologies at Eli Lilly and Company.

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## Considerations and Limitations for Assay Development

William Janzen

*Epizyme, Inc., Cambridge, MA, USA*

The transition from a target to a hit compound can take many paths. Whether the discovery program is developing a pharmaceutical, an academic probe, cosmetics, pesticides, or a toxicity monitoring assay, the development of an assay (or screen) focuses on generating a method that will reliably deliver reproducible results over a period of weeks, months or years, and generate consistent results for every test along the way. Whether you are applying HTS, computational analysis or co-factor analogs, you cannot measure differences without a valid cascade of assays to support hit progression. Assay development principles will be discussed, including detection technologies and logistics as well as the importance of assay validation.

## **SESSION II**

### **Hit Selection and Lead Optimization**

**Chair: D. Martin Watterson, PhD — Northwestern University**

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#### **Session Overview**

D. Martin Watterson, PhD — Northwestern University

#### **From HTS through Hit Identification and Evaluation: Considerations and Best Practices**

Thomas Chung, PhD — Sanford-Burnham Medical Research Institute

#### **Learning from Precedents: Project Flow in Early Stage Small Molecule Refinement for CNS Drug Discovery**

D. Martin Watterson, PhD — Northwestern University

#### **PK/PD in Preclinical Development**

Barry Greenberg, PhD — University Health Network

## SESSION II: Hit Selection and Lead Optimization

### Thomas Chung, PhD, Sanford-Burnham Institute for Medical Research



Thomas D.Y. Chung (aka “T.C.”), PhD, is currently the Director of Outreach, Partnerships & Strategic Alliances for the Conrad Prebys Center for Chemical Genomics at the Sanford-Burnham Institute for Medical Research, responsible for the development and management of collaborative relationships with various academic partners. Previously he was also Project Manager for the Prebys Center’s role as one of the four comprehensive Molecular Libraries Probe Production Centers Network (MLCPN) of the NIH Molecular Libraries Program (MLP), where he was responsible for delivering on NIH-funded and approved chemical probe project against molecular targets associated with disease processes in collaboration with principal investigators. Dr. Chung is a veteran of several major pharmaceutical and life science biotechnology companies and has a multidisciplinary background. He has served in positions of

increasing responsibility: in the Departments of Medicinal Chemistry and Molecular Pharmacology at SmithKline & French Research Laboratories (presently, GlaxoSmithKline); in Virology with Merck Sharp & Dohme and Bristol-Myers Squibb; as a Research Fellow with Pharmacoepia, premier start-up in combinatorial chemistry and highthroughput screening technologies; as Sr. Director of the Leads Discovery Group at DuPont Pharmaceuticals (co-authored the “Z-factor”, the most cited reference in assay development & HTS); and as Chief Scientific Officer an early stage drug discovery technology platform company. Dr. Chung received his B.S. in chemistry from the Massachusetts Institute of Technology in 1978, completed a year of graduate chemistry studies at Stanford University, followed by a year with the Biosciences group at Exxon Research and Engineering in New Jersey, working on metal catalyzed biotransformations. Dr. Chung received his Ph.D. in chemistry from the University of California at Berkeley in 1986, where his thesis work concentrated on metal coordination complexes, metal ion chelation and transport in biology with Prof. Kenneth N. Raymond.

Dr. Chung has published over 45 research papers, authored 6 book chapters in the fields of high-throughput screening, drug discovery, virology, bioinorganic chemistry, structures of metal coordination complexes, authored 53 MLP Probe Reports, and has three issued patents and several provisional patent applications. He is President-Emeritus of the Society for Biomolecular Screening, and was Scientific Advisory Board member for Spotfire a premier data visualization provider, EKM a electronic notebook company, and is on the SAB of Oyagen. He has served on 5 SBIR/STTR review panels, a UI9 Special Emphasis Panel on Natural Products, on the grant review panel for the Alzheimer’s Disease Foundation and is an active advisor, consultant and thought leader in the HTS and technology development fields targeted to the life science industries.

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## From HTS through Hit Identification and Evaluation: Considerations and Best Practices

Thomas Chung

*Conrad Prebys Center for Chemical Genomics, Sanford|Burnham Medical Research Institute, La Jolla, CA, USA*

Many academic institutes have extended their mission from fundamental basic research into more translational and nascent drug discovery activities, comprising high-throughput screening (HTS) of large chemical libraries to identify initial “hits” then discerning which of these are non-artifactual, potent, specific and selective, and more importantly represent authentic and tractable chemical scaffold(s) upon which to base a significant “lead optimization” program. While these processes are routine and standard in the pharmaceutical discovery team, many academic principal investigators are often not prepared for the requirements “at scale” of these highthroughput processes that interrogates hundreds of thousands of compounds per day, confirmation of thousands of hits, and parallel dose response analyses of hundreds of compounds, and the sequential logic of each “triage” step through a “testing funnel” of secondary and tertiary assays. This presentation will provide an process map of biological and assay format considerations of the primary, secondary and tertiary assays that comprise these testing funnels, chemical considerations for chemical tractability, and best practices thereof illustrated with specific examples of CNS target drug discovery programs from our nine year tenure as a comprehensive screening center with the NIH Molecular Libraries Initiative/Program.

## SESSION II: Hit Selection and Lead Optimization

### CHAIR

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



Martin Watterson, PhD, holds the G.D. Searle Endowed Chair Professorship at Northwestern University and is a Professor of Pharmacology in the Northwestern University Feinberg School of Medicine.

Dr. Watterson's previous academic service includes the founding of a successful academic drug discovery training and research program, with alumni in diverse careers and CNS drug candidates taken into preclinical and clinical development. Previous administrative service at Northwestern includes experience as a Department Chair, University Center Director and Curriculum Co-Director. Earlier academic appointments include 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 an Investigator in the Howard Hughes Medical Institute.

Relevant industry experience includes small business start-ups, board of director service and pharmaceutical industry collaboration and consulting. Dr. Watterson currently serves in an advisory capacity to industry, government agencies, and research institutes in the areas of drug discovery and preclinical drug development, translational research, and life sciences. His ongoing research program encompasses collaborative preclinical and clinical development of novel CNS drug candidates emerging from his laboratory, novel target validation in the areas of microvascular disorders and oncology, and a continuing basic science program in calmodulin and protein kinase mediated signal transduction.

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### Learning from Precedents: Project Flow in Early Stage Small Molecule Refinement for CNS Drug Discovery

D. Martin Watterson

*Northwestern University, Chicago, IL, USA*

A critical component of innovation in drug discovery is the development of novel chemical matter for explicit indications and regulated use. The chemical matter can range from small organic molecules, the continuing major form of approved drugs, to macromolecules, predominately proteins among approved drugs. A common theme in the preclinical development process is the anticipation of the downstream regulatory approval stage. In this regard, the “end justifies the means” when it comes to project planning rationale and details of experimental design. Each campaign requires strategic decisions at critical phases of the preclinical development process. One early critical phase is the shift from interesting targets and hits delivered by discovery research to increased target validation through engagement by candidate compounds and the derisking of best-in-class deliverables. Medicinal chemistry refinement and optimization at this critical phase has a major impact on later stage pharmacokinetics, pharmacodynamics, efficacy outcomes and safety evaluations. The campaign goal for this stage is the generation of deliverables with strong potential for later stage regulatory approval. Contemporary approaches to this recursive phase of development tend to address the highest risk aspects of development in conjunction with improving pharmacological function. For example, tractability for metabolic stability and tissue exposure can drive experimental design at this stage. In the case of structure-assisted approaches for single molecular targets, a balance is sought between retention of target affinity and selectivity, improvement in adsorption and metabolism, and a parallel reduction of potential for adverse events. Multi-disciplinary teams often address the multifaceted goal in the design phase through the use of probability based on curated databases of previous drug development success, and in the compound refinement phase through the use of facile experimental screens for pharmacological activities. Case studies will be used to illustrate how downstream regulatory approval considerations and early stage campaign risk reduction can influence experimental design. The didactic intent of the presentation and discussions is to generate awareness for the non-specialist of key team considerations at this critical phase for preclinical development of CNS drug candidates.

## SESSION II: Hit Selection and Lead Optimization

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**Barry Greenberg, PhD**, Toronto Dementia Research Alliance, Toronto Western Research Institute and University Health Network



Barry Greenberg, PhD, has been involved in Alzheimer's disease research and drug discovery since 1985. He has held a series of positions internationally in the US, Sweden and Canada within the biotechnology and pharmaceutical industries.

Dr. Greenberg was the leader of a drug discovery project at AstraZeneca through lead optimization, involving up to 50 individuals from eight departments. Before joining UHN as Director, Neuroscience Drug Discovery and Development, he was Senior Director of Pharmacology at Neurochem, responsible for the preclinical biology research program and a contributor to the analyses of the phase III Alzhemed trial. At UHN, he is also Strategy Director of the Toronto Dementia Research Alliance, a consortium involving academic research and the five memory clinics at hospitals affiliated with the University of Toronto to create a citywide dementia research center. He possesses a significant background in most aspects of the drug discovery process in neurological disease, with externally recognized expertise ranging from target identification and validation through preclinical and clinical development including issues of biomarker-based diagnosis and proof of concept. He has a strong international network in the Alzheimer field including industry, academia, government and the voluntary sector, plus previous involvement in multi-sector consortia.

Dr. Greenberg was a member of the committee charged with drafting the scientific strategic recommendations to inform the National Alzheimer Plan in the US in 2012, and has been appointed as Chair of the Executive Committee for the upcoming follow-up Alzheimer Research Summit at the NIA in February 2015. He has authored or co-authored 70 articles in peer-reviewed journals and 19 book chapters and reviews.

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### PK/PD in Preclinical Development

Barry Greenberg

*Neuroscience Drug Discovery and Development, University Health Network, Toronto, Ontario, Canada*

In preclinical drug development, it is critical to ascertain that an exploratory therapeutic compound reaches its molecular target, or its target tissue in the case of phenotypic screens, at appropriate concentrations and with sufficient longevity to mediate its intended biological effect. In vitro experiments are static with respect to target and compound, while in vivo experiments are dynamic, with time-dependent impacts on compound concentration, distribution, and target disposition. High potency alone in prior in vitro assays is insufficient and often irrelevant. Certain attributes should be ascertained in advance of exposing experimental animals to exploratory compounds, such as physicochemical properties suitable for CNS exposure, and stability in microsomal assays. Subsequent in vivo studies must include pharmacokinetic (PK) and pharmacodynamic (PD) assessments to determine whether the compound exposure is sufficient to interact with its target or organ of interest. This is critical information in guiding administration routes and dosing to deliver informative outcomes. Depending on whether a study is exploratory for target engagement or therapeutic for outcomes analyses, the degree to which absorption, distribution, metabolism, excretion, and toxicity (ADMET) are profiled should be prospectively considered as part of the study design. Toxicity considerations are particularly critical in this context to minimize potential off-target phenotypic impacts on outcome measures. Moreover, in vivo studies should be conducted at doses well below those at which adverse events occur, not merely "just below" a toxic exposure level, as slightly sub-toxic systemic doses may also impact on phenotypic outcomes. Therapeutic studies should also include considerations of distribution/exposure of both the parent compound and its metabolites, some of which may have unanticipated activities that impact on outcomes. In summary, PK, PD and ADMET are important to consider in the strategic design of in vivo experiments for translational research, as all human clinical studies are in vivo experiments.

## **SESSION III**

### **Drug Discovery: From Lead to Clinical Candidate**

**Chair: Edward Spack, PhD, Fast Forward, LLC**

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#### **Session Overview**

Edward Spack, PhD — Fast Forward, LLC

#### **Lead to Clinical Candidate: Essential Chemical Development Practices**

Bruce Molino, PhD — Albany Molecular Research Inc. (AMRI)

#### **Early Phase Drug Product Strategies: What Formulation Strategy is Best for Your Goals?**

Bryan Knox — Pharmatek

#### **Requirement for an IND and Early Considerations**

Edward Spack, PhD — Fast Forward, LLC

#### **Virtual R&D Operations — How to work with CROs and Consultants**

Tilman Brotz, PhD — Achaogen, Inc.

#### **ADDF ACCESS & Young Investigator Scholarship Awards Presentation**

Lauren Friedman, PhD — Alzheimer's Drug Discovery Foundation

## SESSION III: Drug Discovery—From Lead to Clinical Candidate

### **Bruce Molino, PhD, Albany Molecular Research, Inc. (AMRI)**



Bruce Molino, PhD, is currently the Senior Director of Medicinal Chemistry at Albany Molecular Research, Inc. (AMRI) with responsibility for contract discovery chemistry services in Albany NY.

He has established a successful track record in drug discovery spanning nearly 30 years in pharmaceutical R&D. In his 16th year with AMRI, Dr. Molino has successfully managed contract drug discovery teams in pursuit of novel drug molecules for the treatment of a wide range of diseases and therapeutic areas with emphasis on CNS targeted approaches. Dr. Molino played an important leadership role in the AMRI drug discovery collaboration with Bristol-Myers Squibb that led to the advancement of two drug compounds into human clinical trials for treatment of Major Depressive Disorder. BMS-820836, the most advanced candidate, has recently completed phase II clinical trials. Further advancement of this compound is in planning stages.

AMRI's Medicinal Chemistry department is currently engaged in collaboration with the National Institute of Neurological Disorders and Stroke (NINDS) on the Blueprint initiative for which Dr. Molino provides management oversight for AMRI's integrated drug discovery services. The Blueprint initiative provides support for drug discovery approaches initiated in academia and small businesses with the goal to advance novel medicines for treatment of CNS based disorders and diseases. Prior to employment with AMRI, Dr. Molino was a Director in the Medicinal Chemistry Department of Rhône-Poulenc Rorer (known today as Sanofi-Aventis) for more than 10 years. Dr. Molino's contributions at RPR led to the advancement of two clinical candidate compounds in the cardiovascular and thrombosis therapeutic areas. He also led a Respiratory/Inflammation Medicinal Chemistry team at a research center located in the United Kingdom while working at RPR.

Dr. Molino currently serves on the scientific review board of the Alzheimer's Drug Discovery Foundation.

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### **Lead to Clinical Candidate: Essential Chemical Development Practices**

Bruce Molino

*Albany Molecular Research, Inc. (AMRI), Albany, NY, USA*

The presentation will focus on key chemical development principles and practices widely used in the industry to progress small molecule drug compounds into human clinical trials. Important chemistry decisions must be made during this stage to keep compound supply off of the critical path in preclinical development. Simultaneously, one must balance speed and cost considerations when deciding to use GLP or GMP quality material for the IND-enabling toxicology studies. The logic and implications of chemical development practices will be discussed.

## SESSION III: Drug Discovery—From Lead to Clinical Candidate

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### Bryan Knox, Pharmatek



Bryan Knox is a Senior Director of Pharmatek, a contract dosage form development and GMP manufacturing organization. He has a broad background in preclinical and clinical drug development and manufacturing of small molecules and peptides. Mr. Knox's nineteen years of pharmaceutical industry experience include managing hundreds of oral formulation and analytical development projects, controlled release and amorphous dispersion formulations development, process scale up and technology transfer.

He earned his MBA from the University of California San Diego's Rady School of Management and his bachelor of science in biochemistry from the University of California, San Diego.

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### Early Phase Drug Product Strategies: What Formulation Strategy is Best for Your Goals?

Bryan Knox

*Pharmatek, San Diego, CA, USA*

With fewer Phase I candidates making it to proof of concept, it's important to have the appropriate strategy in place for your early phase development. Pharmatek's Bryan Knox will discuss how reaching first-in-human clinical studies quickly is often critical, especially for companies with limited budgets or investor milestones tied to this step. A phase-appropriate approach to development will get you from the bench to the clinic quickly. Of equal importance is the creation of a formulation that will give your candidate the best chance at success. From bioavailability enhancement technologies for insoluble compounds to API-in-a-capsule, this presentation covers multiple development strategies, including:

- Why understanding different formulation strategies is important to the long-term success of your compound.
- Strategies for oral and injectable drugs.
- Strategies for poorly soluble compounds.
- Identification of GLP toxicology and clinical formulations.
- Where can formulations help, and where should medicinal chemistry take a leading role.

## SESSION III: Drug Discovery—From Lead to Clinical Candidate

### CHAIR

**Edward Spack, PhD, Fast Forward, LLC**



Edward Spack, PhD, received his doctoral degree from The Johns Hopkins University and his postdoctoral fellowship in cellular immunology at Stanford University. He worked in San Francisco Bay area biotech companies and private research institutes for over 20 years developing therapies for neurodegenerative diseases, as well as cancer and infectious diseases, focusing on the transition from discovery to. His translational experience includes leading preclinical development of drug candidates for multiple sclerosis, nosocomial infection, and botulism poisoning.

At SRI International, Dr. Spack directed the PharmaSTART program, a consortium of SRI, Stanford, UC Berkeley, UC San Diego, and UC San Francisco chartered to support translational development. He consulted with the NIH translational core services committee and several NIH institutes on preclinical development and currently serves on several study sections, including the NIA Alzheimer's Disease Drug Development review panel and the NIH/CSR Drug Discovery for the Nervous System review panel.

He is currently a consultant on preclinical development. His current activities include Managing Director at Fast Forward LLC, the translational development arm of the National Multiple Sclerosis Foundation, and consulting for several biotech start-up companies.

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### Requirements for an IND and Early Considerations

Edward Spack

*Fast Forward, LLC, San Francisco, 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) that lay the groundwork for IND-enabling studies; 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.

## SESSION III: Drug Discovery—From Lead to Clinical Candidate

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### Tilmann Brotz, PhD, Achaogen, Inc.



Tilmann Brotz, PhD, is a Biopharma R&D Executive with 20 years of research experience and a career of over 13 years in the biopharmaceutical industry, where he led the development of novel therapies from discovery through Phase 3 clinical development. Dr. Brotz worked extensively with distributed, virtual teams and outsourced numerous projects to CROs and CMOs. He is a reviewer and consultant for the TI Catalyst program at CTSI/UCSF and a member of the ADDF's Scientific Review Board.

Currently he is Senior Director of Development Sciences at Achaogen, Inc., a company focused on the development of novel antibiotics. Prior to Achaogen, he led a successful consulting practice working with emerging biotech companies and investment funds on drug development strategy and virtual R&D operations. As Vice President, Preclinical Research & Development at VIA Pharmaceuticals he repurposed an asthma drug for atherosclerosis. Prior to that he held positions of increasing responsibilities at Renovis, Inc. and at the National Cancer Institute.

Dr. Brotz received his PhD in Animal Physiology/Neuroscience from the University of Tübingen and completed his postdoctoral training at the University of California, Berkeley.

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### Virtual R&D Operations - How to work with CROs and Consultants

Tilmann Brotz

*Achaogen Inc., South San Francisco, CA, USA*

Virtual R&D operations have become an important and growing part of biotech and even Pharma business models, shifting significant portions of R&D budgets towards outsourcing activities. We will discuss options to address typical outsourcing needs, how to find the right CRO partner and ways to best integrate the CRO team with your in-house project team and external consultants. We'll look at challenges for preclinical as well as clinical programs and the specific expertise needed from consultants at the different stages of drug development.

# ADDF ACCESS & Young Investigator Scholarship and Awards Presentation

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## Lauren Friedman, PhD, Alzheimer's Drug Discovery Foundation



Lauren Friedman, PhD, is the Scientific Program Manager at the ADDF where she is responsible for supporting management of the ADDF drug discovery portfolio by providing scientific and strategic review of preclinical drug discovery proposals. Additionally, she manages the ADDF ACCESS program, which provides scientists with resources and services to expedite drug discovery research and development.

Dr. Friedman completed her postdoctoral training at Columbia University where she studied modulators of autophagy in Alzheimer's disease. She earned a PhD in Neuroscience at Icahn School of Medicine at Mount Sinai where she studied molecular mechanisms underlying the development and degeneration of brain circuits involved in autism and Parkinson's disease. Dr.

Friedman received a BS in Biopsychology from Tufts University. She has authored numerous peer-reviewed publications and is a member of the Society for Neuroscience, New York Academy of Sciences, and the Association for Women in Science.

## DAY 3: Welcome Notes

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### **Diana Shineman, PhD, 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 \$2 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. She joined the ADDF in 2008.

Dr. Shineman 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.

Dr. Shineman 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, she has also authored numerous articles and peer reviewed publications.

## DAY 3: Keynote Lecture

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### Anne Bang, PhD, Sanford-Burnham Medical Research Institute



Anne Bang, PhD, works on translational research and development utilizing hESC and hiPSC for cell therapy and drug discovery applications. In June 2010, Dr. Bang was recruited by the Sanford Burnham Institute, as Director of Cell Biology, to lead efforts to develop stem cell based disease modeling at the Conrad Prebys Center, a state of the art drug screening facility.

Dr. Bang's experience in stem cell biology began in 2005 at ViaCyte, Inc., where, as Director of Stem Cell Research, she managed an interdisciplinary group working to develop hESC as a source of pancreatic cells for the treatment of diabetes.

She received a BS from Stanford University, a PhD from UCSD, and was a post-doc and Senior Scientist in the Neurobiology Laboratory at the Salk Institute.

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### Utilizing hiPSC-derived Differentiated Cells for High-throughput Drug Screening

Anne Bang

*Sanford-Burnham Medical Research Institute, La Jolla, CA, USA*

Patient specific induced pluripotent stem cells (iPSC) complement traditional cell-based assays used in drug discovery and could aid in the development of clinically useful compounds. They allow interrogation of differentiated features of human cells not reflected by immortalized lines, and importantly they carry disease-specific traits in complex genetic backgrounds that can impact disease phenotypes. Development of technology platforms to perform compound screens of iPSC with relatively high-throughput will be essential to realize their potential for disease modeling and drug discovery. Towards this goal, we have been working to develop a standardized battery of assays against which iPSC-derived neurons can be screened for specific phenotypes. We will discuss our screening results and development of hiPSC based models for testing of drugs on disease relevant cell types.

## **SESSION IV**

### **Strategies for CNS Targets – Case Study Examples**

**Chair: Marcie Glicksman, PhD, Orig3n**

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#### **Session Overview**

##### **Case Study: The Identification of Klotho Enhancers**

Marcie Glicksman, PhD — Orig3n, Inc.

##### **CP2: Generating New Intellectual Property**

Eugenia Trushina, PhD — Mayo Clinic

##### **Meeting Regulatory and Commercialization Challenges in Advancing Agb101 to Slow Progression in Amnestic Mild Cognitive Impairment Due to Alzheimer's Disease**

Michela Gallagher, PhD — AgeneBio, Inc.

##### **Generating Proof of Concept for Alzheimer's Disease Using an Orphan Indication**

Brandon Wustman, PhD — Orphi Therapeutics

##### **Allopregnanolone: From Laboratory Discovery to Clinical Trial**

Roberta Diaz Brinton, PhD — University of Southern California

## SESSION IV: Strategies for CNS Targets

### CHAIR

**Marcie Glicksman, PhD, Orig3n, Inc.**



Marcie Glicksman, PhD, has just taken a new position as Vice President Biology at Orig3n, Inc. Formerly she was the Co-Director of the Laboratory for Drug Discovery in Neurodegeneration (LDDN) an academic drug discovery center at Brigham and Women's Hospital and Harvard Medical School focused on central nervous system diseases. Dr. Glicksman has extensive experience in assay development, high throughput screening, as well as animal pharmacology and preclinical development.

She has been in the field of drug discovery for more than 20 years, the most recent ten years at LDDN and thirteen years in the pharmaceutical industry. Previously, she was at the company, Descartes Therapeutics focused on pain therapeutics and Cubist focused on anti-infectives. Prior to these positions, she was at DuPont-Merck and at Cephalon, Inc. She has led multiple advanced programs for neurodegenerative diseases including co-inventorship of CEPI347, a drug candidate directed at a kinase that has been in Phase III clinical trials.

Dr. Glicksman was elected (2005-2009) to the Board of Directors and served as Chairman of the Society for Biomolecular Sciences (now Society for Laboratory Automation and Screening). She is on the science advisory board for the Alzheimer's disease foundation (ADDF) and the California Institute for Regenerative Medicine (CIRM), and reviews grants for ADDF, NIH, the Michael J Fox and Rett Foundations, and Alzheimer's Association. She also regularly consults and this has included filing an Investigational New Drug application with the FDA, as well as projects involving the development of new technologies.

Dr. Glicksman received a bachelor's degree from Brown University and a PhD degree from Washington University.

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### Case Study: The Identification of Klotho Enhancers

Marcie Glicksman

*Laboratory for Drug Discovery in Neurodegeneration Brigham and Women's Hospital and Harvard Medical School, and Biology at Orig3n, Inc., 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 identifying activators of the protein klotho will be presented highlighting the basis for the decision-making strategy from assay development through animal studies.

## SESSION IV: Strategies for CNS Targets

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### Eugenia Trushina, PhD, Mayo Clinic



Eugenia Trushina, PhD, is an Associate Professor in the Department of Neurology and Department of Molecular Pharmacology and Experimental Therapeutics at the Mayo Clinic Rochester. She received her doctoral degree in organic chemistry from Saratov State University in Russia.

Dr. Trushina completed her postdoctoral training at the Mayo Clinic, Rochester where she worked with Drs. C. McMurray, R. Pagano and M. McNiven studying mechanisms of multiple neurodegenerative diseases including Huntington's (HD) and Alzheimer's Diseases (AD).

Dr. Trushina's research program is focused on the understanding early molecular mechanisms of neurodegeneration, with the emphasis on the role mitochondria play in health and disease. Her current research projects involve the development of new mitochondria-targeted therapeutic approaches.

Dr. Trushina is a recipient of the NIH, BrightFocus, GHR, ADDF and Mayo Clinic Research Awards.

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### CP2: Generating New Intellectual Property

Eugenia Trushina

*Mayo Clinic Rochester, Rochester, MN, USA*

Modulation of mitochondrial function could be beneficial in various diseases. We found that treatment with novel metabolic modulator tricyclic pyrone compound CP2 significantly delays the development of Alzheimer's disease in multiple transgenic animal models. I will discuss what steps were taken to successfully progress from the level of lead identification to the development of novel patentable compounds with superior properties from the point of view of the academic scientist.

## SESSION IV: Strategies for CNS Targets

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**Michela Gallagher, PhD, AgeneBio, Inc.**



Michela Gallagher, PhD, rose through the faculty ranks at University of North Carolina at Chapel Hill, where she was the Kenan Professor of Psychology prior to joining Johns Hopkins University in 1997. She has published over 250 peer-reviewed papers, has been the recipient of a Senior Research Scientist Award from NIMH (1990-1999), a Freedom to Discover Award from the Bristol-Myers Foundation (2003-2008), and Senior Scientist Award from the Ellison Medical Foundation (2008- 2012) and is the 2014 recipient of the Mike Salpeter Lifetime Achievement award from the Society for Neuroscience. She is a fellow of the American Psychological Association, the American Psychological Society, and the American Association for the

Advancement of Science. She has served the on Boards of Scientific Counselors at the National Institute of Mental Health and the National Institute on Aging. She chaired the Department of Psychological and Brain Sciences at Johns Hopkins from 2000-2007 and then served a term as Vice Provost of the Faculty and Academic Affairs at Johns Hopkins University.

Dr. Gallagher is the Director of the Neurogenetics and Behavior Center at Johns Hopkins University and heads a multi-institutional research program funded for over 20 years by the National Institute on Aging. Her scientific work established a model for neurocognitive aging that shifted research from studies of neurodegeneration as a cause of memory loss in normal aging to uncovering functional mechanisms and, more recently, led to a successful translational program in patients with mild cognitive impairment, a condition that is transitional between normal aging and Alzheimer's disease.

She is the Founder of AgeneBio, Inc. a Biotechnology Company located in Baltimore, Maryland, which is advancing therapeutics to treat amnesic mild cognitive impairment.

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### **Meeting Regulatory and Commercialization Challenges in Advancing Agb101 to Slow Progression in Amnesic Mild Cognitive Impairment Due to Alzheimer's Disease**

Michela Gallagher

*AgeneBio, Inc., Baltimore, MD, USA*

No therapy to treat aMCI symptomatically or to slow progression to Alzheimer's disease (AD) dementia has yet received FDA approval. AgeneBio, Inc was founded to develop a therapeutic for aMCI to address the critical unmet need for this large and growing population of patients. AgeneBio's clinical stage program will be the first Phase III randomized controlled, multi-site, clinical trial to target the condition of hippocampal hyperactivity, which characterizes the clinical stage of aMCI and predicts progression to dementia. The treatment in this two-year protocol will be AGB101, an extended release formulation of low-dose levetiracetam. While the therapeutic rationale is grounded in extensive preclinical and clinical data, the company's meetings with the FDA (2012-2014) were essential in addressing the absence of a defined regulatory pathway in the aMCI stage of disease. Considerable work by the company also focused on the development of AGB101 as a 'New Therapeutic Entity' suitable for commercialization. This workshop presentation will discuss AgeneBio's progress in addressing these key hurdles in an Alzheimer's drug discovery and development program from the perspective of an academic founder.

## SESSION IV: Strategies for CNS Targets

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### Brandon Wustman, PhD, OrPhi Therapeutics



Brandon Wustman, PhD, is the CEO and co-founder of OrPhi Therapeutics in San Diego, California. OrPhi Therapeutics is developing small molecule pharmacological chaperone therapies for the treatment of diseases affecting the CNS. OrPhi's lead molecule, OT1001, is currently in late preclinical development for the treatment of a rare inherited form of Cerebral Amyloid Angiopathy.

Prior to OrPhi, Dr. Wustman led drug discovery efforts at Amicus Therapeutics for the development of pharmacological chaperones and next generation enzyme replacement therapies for lysosomal storage disorders and neurodegenerative diseases. These studies contributed to the development of 2 pharmacological chaperone (PC) therapies in preclinical development for Parkinson's disease and Alzheimer's disease, 2 enzyme replacement therapies (ERTs) in preclinical development for the lysosomal storage disorders Pompe disease and Mucopolysaccharidosis type I, and 5 therapies (3 PC therapies and 2 PC/ERT combination therapies) in clinical development for the treatment of Fabry disease, Gaucher disease and Pompe disease.

During his tenure at Amicus, Dr. Wustman's team also discovered biochemical links between common neurodegenerative diseases such as Parkinson's and Alzheimer's, and rare lysosomal storage disorders including Gaucher disease, Tay-Sachs disease, Sandhoff disease and GMI Gangliosidosis.

Dr. Wustman received a "Therapeutics Initiative Grant" from the Michael J. Fox Foundation in 2006, and a "Preclinical Drug Discovery Grant" from the Alzheimer's Drug Discovery Foundation in 2010 to further investigate the use of chaperones for the treatment of Parkinson's and Alzheimer's, respectively.

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### Generating Proof of Concept for AD Using an Orphan Indication

Brandon Wustman

*OrPhi Therapeutics, San Diego, CA, USA*

Using an Orphan Indication Gangliosides are a type of lipid found in cell membranes and growing evidence indicates that abnormalities in ganglioside metabolism may contribute to cerebral amyloidoses by accelerating the generation of neurotoxic forms of A $\beta$  on the surface of membranes within cells. In support of this, we found that brains from human subjects with GM1 and GM2 gangliosidoses (i.e., Tay Sachs disease, Sandhoff disease) accumulate intraneuronal A $\beta$  and ganglioside-bound A $\beta$ . Gangliosides, including GM2, have been shown to accumulate in sick neurons and promote in vitro assembly of wild-type and mutant Alzheimer's amyloid- $\beta$  (A $\beta$ ) peptides. It has also been suggested that these gangliosides might modulate regional A $\beta$  deposition, notably, within neurons and the cerebrovasculature. Within the cerebrovasculature, A $\beta$  deposition is mainly associated with smooth muscle cells, where GM2 and GM3 gangliosides are abundant. The Dutch APPE693Q mutant form of A $\beta$  causes a hereditary form of cerebral amyloid angiopathy and, in vitro, shows a particular susceptibility to the pro-aggregation properties of GM2 and GM3 gangliosides. Taken together, we hypothesized that increasing  $\beta$ -hexosaminidase ( $\beta$ -hex) activity would lead to a reduction in GM2 levels, which in turn, would cause a reduction in A $\beta$  aggregation and accumulation. The small molecule OT1001 is a  $\beta$ -hex-targeted pharmacological chaperone with good bioavailability, blood-brain barrier penetration, high selectivity for  $\beta$ -hex, and low cytotoxicity. Dutch APPE693Q transgenic mice accumulate oligomeric A $\beta$  as they age, as well as A $\beta$  oligomer-dose-dependent anxiety and impaired novel object recognition (NOR). Treatment of Dutch APPE693Q mice with OT1001 caused a dose-dependent increase in brain  $\beta$ -hex levels up to 3-fold over those observed at baseline. OT1001 treatment was associated with reduced anxiety, improved learning behavior in the NOR task, and dramatically reduced intraneuronal GA $\beta$  accumulation in the subiculum and perirhinal cortex, both of which are brain regions required for normal NOR. These data indicate that increasing  $\beta$ -hex activity could be useful for management of human cerebral amyloidoses, particularly those associated with certain APP/A $\beta$  mutations, such as Dutch CAA.

## SESSION IV: Strategies for CNS Targets

### 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 1b 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- $\beta$  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 1b 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.

## **SESSION V**

### **Developing Science into Products**

**Chair: Frank Longo, MD, PhD — Stanford University and Pharmatrophix**

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#### **Session Overview**

Frank Longo, MD, PhD — Stanford University & Pharmatrophix

#### **Models for Technology Translation: Innovative Incubator Models**

Guy Seabrook, PhD — Johnson & Johnson Innovation

#### **Intellectual Property Strategies: What and When to File for Patent Protection**

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

#### **A New Paradigm for Translational Research**

James Schaeffer, PhD — California Institute for Biomedical Research (Calibr)

#### **Developing a Biotechnology Company out of Academia**

Frank Longo, MD, PhD — Stanford University & Pharmatrophix

#### **Panel Discussion: Novel Opportunities for Identifying a Development Partner**

MODERATOR: Frank Longo, MD, PhD — Stanford University & Pharmatrophix

Mark Allegretta, PhD — National Multiple Sclerosis Society

Michela Gallagher, PhD — AgeneBio

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

James Schaeffer, PhD — California Institute for Biomedical Research (Calibr)

Guy Seabrook, PhD — Johnson & Johnson Innovation

# SESSION V: Developing Science into Products

## Guy Seabrook, PhD, Johnson & Johnson Innovation



Guy Seabrook, PhD, joined Janssen Pharmaceutical Companies of Johnson & Johnson in 2012. His role as the Neuroscience Lead for the newly formed Johnson & Johnson California Innovation Center is to help co-create and implement the external innovation plan to deliver the Neuroscience Therapeutic Area R&D Strategy. This includes solidifying Janssen's place as an ideal partner in a highly competitive landscape of external collaborations. Our goals are to identify the best opportunities for value-generating collaborations and develop an industry-leading portfolio of investment opportunities. This involves the cultivation of a strong scientific network of experts in the global innovation community. He has over 23 years drug discovery research which includes preclinical research on marketed products and candidates in clinical development. Formerly, Guy was part of Eli Lilly's Global External Research & Development (GER&D) organization where he led the GER&D team for the Lilly Bio-Medicines Business Unit, and also at Merck

& Co, Inc where he was the Head of the West Point Department of Alzheimer's Disease Research. He graduated with a PhD in Zoology from the University of Nottingham UK (1987), and completed his postdoctoral research at the University of Miami School of Medicine USA.

### Recent deals:

- August 7th 2014. Neuroscience Catalyst Program. University of Toronto, Canada. Multi-year Collaborative Research Agreement on Alzheimer's disease & Mood disorders.
- July 3rd, 2014. NewCo seed funding w/ JJDC. Undisclosed.
- June 19th, 2014. Research collaboration and option agreement with BrainStem Biometrics, Inc. <http://www.prnewswire.com/news-releases/johnson--johnson-innovation-catalyzes-new-and-exciting-science-and-technology-in-pharmaceutical-medical-device-diagnostic-and-consumer-healthcare-spaces-263794901.html>
- Mar 10th, 2014. NCIRE. The Brain Health Registry. <http://www.brainhealthregistry.org/>
- Dec 19th, 2013. Alector. Research Collaboration Agreement. <http://www.prnewswire.com/news-releases/alector-teams-up-with-johnson--johnson-innovation-to-explore-novel-alzheimers-target-249260671.html>
- Dec 19th, 2013. Undisclosed Academic University. Multi-year Collaborative Research Agreement on Alzheimer's disease.
- Nov 1st, 2013. Evotec. Research Collaboration and License Agreement on Alzheimer's disease. <http://www.fiercebitech.com/press-releases/evotecannounces-targetad-collaboration-johnson-johnson-innovation-identify>
- April 4th, 2013. Government of Canada, as represented by the Consulate General of Canada, San Francisco. The Cognition Challenge. <http://www.prnewswire.com/news-releases/johnson--johnson-innovation-announces-finalists-of-cognition-challenge-214881321.html>

## Models for Technology Translation: Innovative Incubator Models

Guy Seabrook

*Johnson & Johnson Innovation, Menlo Park, CA, USA*

Science and technology are creating unprecedented opportunities to transform healthcare. Close partnerships between academia, biotech, venture, and industry provide the fundamental basis for delivering innovative healthcare solutions to patients. Effective external innovation strategies are imperative to adapt to new science, disruptive technologies, and discoveries that can help jump-start new projects, replace old or non-competitive ideas, as well as leverage external capital to spread risk and expand investments. Scientific breakthroughs rarely align neatly with "areas of interest". The most important medicines of our decade will come from unpredictable sources and in challenging areas of drug discovery like Neuroscience.

At Johnson & Johnson Innovation our goals are to identify the best opportunities for value-generating collaborations and develop an industry-leading portfolio of partnership and investment opportunities. This involves the cultivation of a strong scientific network of experts in the global innovation community. But, signing a deal is only the start. For example, in collaboration with the University of Toronto we have facilitated a new strategic partnership with the Collaborative Center for Drug Research called the Neuroscience Catalyst program. This agreement will help identify and validate new therapeutic targets to advance clinical treatment for major brain disorders focused on Alzheimer's disease and Mood disorders. Externally recognized as being "a very refreshing contrast to the usual industry modus operandi" (NeuroPerspective October 2014 No.227) this collaboration provides translational seed funding and in-kind resources to help academic entrepreneurs generate data that will attract downstream financing to support generation of new businesses and energize the innovation ecosystem. The scope and structure of this incubation model will be discussed as well as the implications for future models aimed at translating technological discoveries across the life sciences.

## SESSION V: Developing Science into Products

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



Leslie Meyer-Leon, PhD, JD, 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.

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### Intellectual Property Strategies: What and When to File for Patent Protection

Leslie Meyer-Leon

*IP Legal Strategies Group PC, Boston, MA, USA*

A strong intellectual property (IP) position remains critical for competitive positioning, financing, 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 discuss which inventions are still eligible for, and worthy of, patent protection. We will also discuss how early in the development cycle to file your patent application, and how much you need to disclose to obtain patent claims that are commercially worthwhile.

## SESSION V: Developing Science into Products

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**James Schaeffer, PhD**, California Institute for Biomedical Research (Calibr)



James Schaeffer, PhD, joined the California Institute for Biomedical Research (Calibr) as VP of External Relations in June 2014 following a 25 year career at Merck Research Labs. During his first 15 years at MRL, he directed research groups focusing primarily on neuroendocrinerelated projects. Jim moved to San Diego in 2004 to assume the role of Merck's "Science Scout" on the West Coast, with the responsibility to identify new opportunities across all therapeutic areas at all stages of development including enabling technologies.

During the next ten years, Dr. Schaeffer was directly involved in the execution of 15 major agreements with West Coast based organizations. Jim was also directly involved in the formation of a partnership between Merck and Dr. Peter Schultz which lead to the establishment of Calibr.

Dr. Schaeffer received his PhD at Baylor College of Medicine and was a post-doctoral fellow in the laboratory of Dr. Julius Axelrod at the National Institute of Mental Health. Prior to joining Merck, he was an assistant professor in the Department of Reproductive Medicine in the School of Medicine at UCSD. He is the author of more than 110 articles in peer reviewed journals.

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### A New Paradigm for Translational Research

James Schaeffer

*California Institute for Biomedical Research, La Jolla, CA, USA*

The development of a robust, early stage pipeline is a high-risk, expensive and long-term endeavor. As a result, over the past several years we have seen virtually every pharma/big biotech announce initiation of 'novel' approaches to 'enhance access to external innovation'. The goal of these initiatives is to effectively mitigate risk and 'increase the number of shots on goal'. The sources for this innovation are predominantly small biotechs and academic labs and the agreements range from collaborations to licenses to acquisitions. This presentation will provide a description of The California Institute for Biomedical Research (Calibr), a non-profit research organization with the mission of translating early-stage scientific discoveries into small molecules and biologics with pharmacological validation in relevant animal models. The success of organizations such as Calibr will ultimately be determined by their ability to consistently advance early stage programs into the clinic. The process of finding the 'right' partner for advancing these projects will be discussed from the perspective of both the 'buyer' and the 'seller'.

# SESSION V: Developing Science into Products

## CHAIR

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

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Frank Longo, MD, PhD, 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 elucidated novel mechanisms and executed translational work pioneering small molecule treatment strategies for Alzheimer's and other neurodegenerative diseases.

In 2005, while at UNC, he founded PharmatropHiX, a company focused on the commercial development of these therapies. A lead candidate compound for Alzheimer's disease has successfully completed phase I human trials and preparations for a phase 2a trial are underway.

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## Developing a Biotechnology Company out of Academia

Frank Longo

*Stanford University and PharmatropHiX, Stanford, CA, USA*

We will review the rationale, challenges and alternatives for academic-based faculty spinning a biotechnology company out of an academic program. Key areas of focus will include the following: approaches for creating technology elements that pharma partners seek (including quality of IP, target rationale/validation/engagement, quality and translational value of preclinical work, availability of relevant biomarkers, clinical trial plans and/or data); options for funding models; working with CROs; large pharma partnership models and goals; and exit strategy options.

## **Panel Discussion: Novel Opportunities for Identifying a Development Partner**

MODERATOR: Frank Longo, MD, PhD — Stanford University & Pharmatropix

Mark Allegretta, PhD — National Multiple Sclerosis Society

Michela Gallagher, PhD — AgeneBio

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

James Schaeffer, PhD — California Institute for Biomedical Research (Calibr)

Guy Seabrook, PhD — Johnson & Johnson Innovation

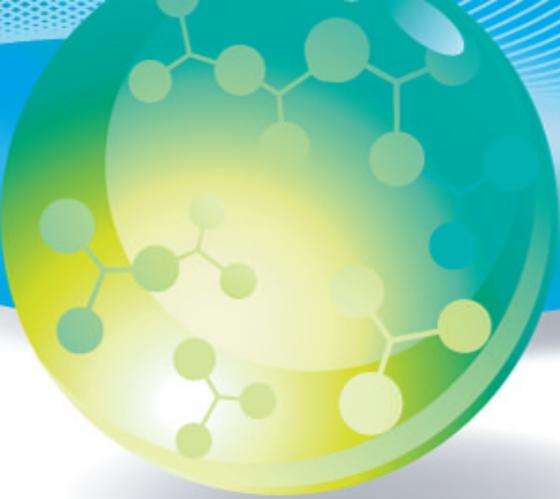
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### **Mark Allegretta, PhD, National Multiple Sclerosis Society**



Mark Allegretta, PhD, is Associate Vice President of Commercial Research at National MS Society. Mark's responsibilities include providing leadership and direction for the Society's commercial research programs and portfolio, including partnerships developed through Fast Forward. He works to engage the academic and commercial research community to develop innovative solutions for MS treatments, and works with other members of the research team to assure integration and alignment of commercial research programs with the Society's overall research portfolio. He joined the Society in 2014 with 28 years of experience in biotechnology and pharmaceutical operations. Most recently, he was President, Chief Scientific Officer and Co-founder of BioMosaics in Burlington, Vermont, where he dealt with all aspects of cancer

biomarker development, licensing deals and business partnerships. Mark earned his Bachelor's degree from Hartwick College and his PhD in Cellular and Molecular Biology from the University of Vermont. He was the recipient of a National MS Society postdoctoral fellowship at Stanford University.



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We are united and inspired by the hope for better lives. Since our founding by Col. Eli Lilly in 1876, we have been committed to discovering solutions to our world's most pressing health problems. More than a century later, we remain true to our founding family's vision and values – to create high quality medicines with integrity, excellence and respect for people. Across the globe, you will find Lilly employees working tirelessly to bring life-changing medicines to people who need them, offering support to patients and families living with serious illness, and giving back to their communities and the environment through countless acts of service.

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

### **Forest Laboratories Inc.**

We develop and manufacture pharmaceuticals of the highest quality. We meet current and future customer needs through smart investments in R&D. We deliver best-in-class service and superior value. We celebrate the many cultures of our global team. We enhance the communities in which we live and work. We build shareholder value in all we do.

### **National Multiple Sclerosis Society**

The National MS Society's vision is: A World Free of MS. The Society's mission is: We mobilize people and resources to drive research for a cure and to address the challenges of everyone affected by MS.

## PARTNERS

**Taub Institute for Research on Alzheimer's Disease and the Aging Brain** is the nucleus of a dynamic, multidisciplinary endeavor. The Institute brings together Columbia University researchers and clinicians to uncover the causes of Alzheimer's, Parkinson's and other age-related brain diseases and to discover ways to prevent and cure these diseases.

**IRBM** was created in 2009 as a spin-off of the Italian Merck Research Laboratories. The team has an impressive productivity having delivered 25 preclinical candidates over 9 years, including small molecule, peptides and synthetic vaccines, currently in clinical development (Isentress, Grazoprevir, Niraparid). The contributions of IRBM to those achievements are documented in over 800 papers and 100 patents. IRBM provides drug discovery solutions from target identification to preclinical candidate identification for both small molecule and peptide therapeutics thanks to integrated platforms and expertise including HTS, peptide and antibody phage display libraries, medicinal chemistry and peptide therapeutics, DMPK and neurosciences.

**PsychoGenics** is a contract research organization in neurobiology, providing state of the art preclinical services (behavior, electrophysiology, immunohistochemistry, imaging, etc.) and mouse models for most CNS disease areas. Neurodegenerative disorders, are our company's core competence. We offer well validated pharmacologically induced and genetically modified disease models, optimizing predictive value of preclinical drug development programs. Our models have been used by leading pharmaceutical/biotech companies and are well documented in current scientific literature. PsychoGenics' cube technologies combine sensitive computer vision and precise robotics and informatics to provide unbiased, high throughput *in vivo* screening for CNS drug discovery and phenotyping.