11th ANNUAL DRUG DISCOVERY FOR NEURODEGENERATION CONFERENCE:
An Educational Course on Translating Research into Drugs

February 12-14, 2017 • San Diego, CA

Presented by the Alzheimer’s Drug Discovery Foundation

www.alzdiscovery.org

#CNSDrugCourse
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# LIST OF ABBREVIATIONS

- **ADMET** (absorption, distribution, metabolism, excretion)
  - Absorption - ability of drug to penetrate the GI tract to the circulatory system
  - Distribution - solubility of drug in blood, binding to plasma proteins
  - Metabolism - chemical modifications of drug (e.g. by cytochrome P), amount available to reach target
  - Excretion - mechanisms of drug elimination from the body
- **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_max =** maximum plasma concentration
  - **T_max =** time to achieve maximum plasma concentration
  - **T_{1/2} =** elimination half-life
  - **F =** percent bioavailability
- **TPP** - Target product profile
ABOUT THE ALZHEIMER’S DRUG DISCOVERY FOUNDATION

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

• The ADDF has granted more than $103 million to fund 564 Alzheimer’s drug discovery programs and clinical trials in academic centers and biotechnology companies in 18 countries.

• As a measure of success, programs funded by the ADDF have gone on to receive commitments of nearly $2 billion in follow-on commitments from the government, pharmaceutical companies and venture capital firms.

• In 2016, the ADDF raised over $24 million to support preclinical drug discovery and clinical development programs. 100% of funds raised went directly to drug research and related scientific programs, thanks to the generosity of a private Lauder Family Foundation that covered all administrative and operational expenses.

OUR CONFERENCES

The Alzheimer’s Drug Discovery Foundation organizes two annual scientific conferences as part of our ongoing efforts to increase researchers’ knowledge about Alzheimer’s disease and the drug discovery process.

Our International Conference on Alzheimer’s Drug Discovery held on September 11-12, 2017 in Jersey City, NJ will bring together academic and industry scientists intent on accelerating the development of innovative treatments for Alzheimer’s disease and related dementias. Top-level scientists in the field and the ADDF’s funded investigators will present on their current research progress and stimulate discussion.

And our Drug Discovery for Neurodegeneration Conference held next year in the Spring in Washington, DC is designed as a comprehensive course on the drug discovery process, from target validation through to clinical development, the 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.
SCIENTIFIC ADVISORY COMMITTEE

Kurt Brunden, PhD, University of Pennsylvania

Howard Fillit, MD, Alzheimer’s Drug Discovery Foundation

Lauren Friedman, PhD, Alzheimer’s Drug Discovery Foundation

Marcie Glicksman, PhD, Orig3n, Inc.

Andrew Koemeter-Cox, Alzheimer’s Drug Discovery Foundation

Frank Longo, MD, PhD, Stanford University

Suzana Petanceska, PhD, National Institute on Aging

Diana Shineman, PhD, Alzheimer’s Drug Discovery Foundation

Edward Spack, PhD, Vector BioSolutions

D. Martin Watterson, PhD, Northwestern University

CONFERENCE DELIVERABLES

A webcast of the entire conference will be made available on the Alzheimer’s Drug Discovery Foundation Conference website (www.worldeventsforum.com/addf/drugdiscovery/videocasts), where you may also access a webcast of last year’s conference.
On behalf of the Alzheimer’s Drug Discovery Foundation (ADDF), I am pleased to welcome you to the 11th Drug Discovery for Neurodegeneration Conference: An Educational Course on Translating Research into Drugs.

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

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

We encourage you to visit the poster presentations which showcase our talented Young Investigator Scholarship and Award winners. Poster presentations are scheduled during the lunch breaks.

Our meeting is made possible by the generous support of our sponsors: National Institute of Aging, Eli Lilly and Company, Merck & Co., Taub Institute for Research on Alzheimer’s Disease and the Aging Brain, Harrington Discovery Institute, The National Multiple Sclerosis Society, and our exhibitors: InterVivo Solutions Inc., Science Exchange, PsychoGenics Inc, Biosensis Pty Ltd, Brains On-line and Collaborative Drug Discovery. We would also like to thank our media partners for their commitment to making this meeting a success.

This year, we are pleased to host the meeting in San Diego, CA, home to 21 Nobel Laureates in 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 densest 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 are proud to welcome attendees from all over the world and are looking forward to a stimulating and educational two and a half days. Thank you for joining us!

Howard Fillit, MD
Founding Executive Director and Chief Science Officer
Alzheimer’s Drug Discovery Foundation
## PROGRAM

All sessions will be held at the DoubleTree by Hilton San Diego Mission Valley as follows:

- **Lectures** will be held in the Great Room V-VIII.
- **Exhibits and Poster Sessions** will be held in the Great Room I-IV.
- **Partnering Sessions** will be held in the North Foyer.
- **Coffee breaks and meals** will be served in the Great Room I-IV.

### Sunday, February 12, 2017

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>2:00pm–4:00</td>
<td>Registration (South Foyer)</td>
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<tr>
<td>4:00–4:20</td>
<td><strong>Welcome &amp; Opening Remarks: Challenges and Opportunities in Academic Drug Discovery</strong></td>
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<td></td>
<td>Howard Fillit, MD—Alzheimer’s Drug Discovery Foundation</td>
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<tr>
<td>4:20–5:00</td>
<td><strong>KEYNOTE LECTURE: Developing Radiotracers to Assess Target Engagement and Beyond in the Brain</strong></td>
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<td>Jacob Hooker, PhD—Harvard Medical School</td>
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<td>5:00–5:10</td>
<td>Q&amp;A</td>
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<td>5:10–7:00</td>
<td>Welcoming Reception (Shutters East I and II)</td>
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### Monday, February 13, 2017

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<tr>
<th>Time</th>
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<tr>
<td>7:30am–8:30</td>
<td>Continental Breakfast</td>
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<tr>
<td>8:30–8:35</td>
<td>Welcome &amp; Opening Remarks</td>
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<tr>
<td></td>
<td>Howard Fillit, MD—Alzheimer’s Drug Discovery Foundation</td>
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<tr>
<td>8:35–8:40</td>
<td><strong>ADDF Funding Opportunities</strong></td>
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<td>Lauren Friedman, PhD—Alzheimer’s Drug Discovery Foundation</td>
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<tr>
<td>8:40–9:00</td>
<td><strong>Bridging the Preclinical to Clinical Gap: An Overview of Translational Research Programs at the NIA</strong></td>
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<td>Lorenzo Refolo, PhD—National Institute on Aging</td>
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<tr>
<td>9:00–9:10</td>
<td><strong>NINDS Opportunities for Translational Research Funding</strong></td>
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<td>Amir Tamiz, PhD—National Institute of Neurological Disorders and Stroke</td>
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I. **Embarking on a Drug Discovery Campaign**  
Chair: Marcie Glicksman, PhD—Orig3n, Inc.

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<tr>
<td>9:10–9:15</td>
<td><strong>Session Overview</strong></td>
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<td>Marcie Glicksman, PhD—Orig3n, Inc.</td>
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<tr>
<td>9:15–9:35</td>
<td><strong>What Makes a Good Target? A Perspective in Neurodegenerative Disease Therapeutic Discovery</strong></td>
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<td>Samuel Hasson, PhD—Pfizer, Neuroscience Unit</td>
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<td>9:35–9:45</td>
<td>Q&amp;A</td>
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<tr>
<td>9:45–10:05</td>
<td><strong>New Trends and Technology in Assay Development</strong></td>
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<td>Marcie Glicksman, PhD—Orig3n, Inc.</td>
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<tr>
<td>10:05–10:15</td>
<td>Q&amp;A</td>
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<tr>
<td>10:15–10:35</td>
<td><strong>Development of Small-Molecule Autophagy Inducers that Mitigate Neurodegeneration</strong></td>
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<td>Steven Finkbeiner, MD, PhD—Gladstone Institute of Neurological Disease</td>
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<td>10:35–10:45</td>
<td>Q&amp;A</td>
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<tr>
<td>10:45–11:15</td>
<td><strong>Exhibitor Session and Break</strong></td>
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II. **Starting at the End: The Pharmacology—Chemistry Interface in Preclinical Drug Development**  
Chair: D. Martin Watterson, PhD—Northwestern University

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<th>Time</th>
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<tr>
<td>11:15–11:20</td>
<td><strong>Session Overview</strong></td>
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<td></td>
<td>D. Martin Watterson, PhD—Northwestern University</td>
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<tr>
<td>11:20–11:40</td>
<td><strong>Medicinal Chemistry for Today’s Biology</strong></td>
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<td>Dario Doller, PhD—Alcyoneus/ScienceWorks</td>
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<tr>
<td>11:40–11:50</td>
<td>Q&amp;A</td>
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<tr>
<td>11:50–12:10pm</td>
<td><strong>Fragment-based Drug Discovery</strong></td>
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<td>Daniel Erlanson, PhD—Carmot Therapeutics, Inc.</td>
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<tr>
<td>12:10–12:20</td>
<td>Q&amp;A</td>
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<tr>
<td>12:20–12:40</td>
<td><strong>Pharmacology Driven Optimization in Candidate Development</strong></td>
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<td>D. Martin Watterson, PhD—Northwestern University</td>
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<tr>
<td>12:40–12:50</td>
<td>Q&amp;A</td>
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<tr>
<td>12:50–1:40</td>
<td>Lunch and Poster Session - All poster presenters should stand by their posters from 1:15 to 1:40pm</td>
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III. **Drug Discovery: From Lead to Clinical Candidate**  
Chair: Edward Spack, PhD—Vector BioSolutions

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<tr>
<td>1:40–1:45</td>
<td><strong>Session Overview</strong></td>
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<td></td>
<td>Edward Spack, PhD—Vector BioSolutions</td>
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<tr>
<td>1:45–2:05</td>
<td><strong>PK/PD in Preclinical Development</strong></td>
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<td>Sharon Rosenzweig-Lipson, PhD—AgeneBio, Inc.</td>
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<tr>
<td>2:05–2:15</td>
<td>Q&amp;A</td>
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</table>
| 2:15–2:35 | Alternative Animal Models for In Vivo Efficacy and Study Design Considerations  
Joseph Araujo—InterVivo Solutions, Inc. |
| 2:35–2:45 | Q&A                                                                   |
| 2:45–3:05 | Drug Delivery for CNS                                                
Ruben Boado, PhD—ArmaGen, Inc. |
| 3:05–3:15 | Q&A                                                                   |
| 3:15–3:45 | Exhibitor Session and Break                                          |
| 3:45–4:05 | Q&A                                                                   |
| 4:05–4:15 | Requirements for an IND                                              
Edward Spack, PhD—Vector BioSolutions |
| 4:15–4:30 | ADFD Young Investigator Scholarship and Awards Presentation        
Andrew Koemeter-Cox, PhD—Alzheimer’s Drug Discovery Foundation |
| 4:45–5:05 | Partnering/Mentoring Session *pre-registration required             |
| 5:05–5:15 | Networking Reception                                                |

Tuesday, February 14, 2017

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<tr>
<td>7:30am–8:00</td>
<td>Partnering/Mentoring Session *pre-registration required</td>
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<tr>
<td>7:30–8:20</td>
<td>Continental Breakfast</td>
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</tbody>
</table>
| 8:20–8:25 | Welcome & Opening Remarks                                           
Diana Shineman, PhD—Alzheimer’s Drug Discovery Foundation |
| 8:25–9:05 | KEYNOTE LECTURE: Adapting the Chemistry and/or Biology of Proteostasis to Ameliorate Protein Aggregation Diseases  
Jeffery Kelly, PhD—The Scripps Research Institute |
| 9:05–9:15 | Q&A                                                                   |

IV. Strategies for Challenging CNS Targets—Case Study Examples
Chair: Kurt Brunden, PhD—Perelman School of Medicine at the University of Pennsylvania

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<th>Time</th>
<th>Event</th>
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</table>
| 9:15–9:20 | Session Overview                                                     
Kurt Brunden, PhD—Perelman School of Medicine at the University of Pennsylvania |
| 9:20–9:40 | Intrathecal Stem Cell Therapy for Multiple Sclerosis                
Violaine Harris, PhD—Tisch Multiple Sclerosis Research Center of New York |
| 9:40–9:50 | Q&A                                                                   |
Kurt Brunden, PhD—Perelman School of Medicine at the University of Pennsylvania |
| 10:10–10:20| Q&A                                                                   |
| 10:20–10:50| Exhibitor Session and Break                                          |
| 10:50–11:10| Preparing for an IND: Case Study in the Development of a Small Molecule for a Neurodegenerative Disorder  
Douglas Bonhaus, PhD—Neuropore Therapies |
| 11:10–11:20| Q&A                                                                   |
| 11:20–11:40| Antisense Oligonucleotides for The Treatment of Huntington’s Disease: Lessons Learned from Mice and Non-Human Primates  
Hien Tran Zhao, PhD—Ionis Pharmaceuticals, Inc. |
| 11:40–11:50| Q&A                                                                   |
| 11:50–12:10| Repurposing Drugs for Neurodegenerative Diseases                    
Albert La Spada, MD, PhD—University of California San Diego School of Medicine |
| 12:10–12:20| Q&A                                                                   |
| 12:20–1:10 | Lunch and Poster Session - All poster presenters should stand by their posters from 12:45 to 1:10 pm |

V. Commercialization Strategies: Developing Science into Products
Chair: Frank Longo, MD, PhD—Stanford University and PharmatrophiX

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<th>Time</th>
<th>Event</th>
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</table>
| 1:10–1:15 | Session Overview                                                     
Frank Longo, MD, PhD—Stanford University and PharmatrophiX |
| 1:15–1:35 | Intellectual Property for Early Stage Life Science Companies         
Laurie McNamara, JD, PhD & Maya Skubatch, JD—Wilson Sonsini Goodrich & Rosati |
| 1:35–1:45 | Q&A                                                                   |
| 1:45–2:05 | Lessons Learned in Drug Development from an Academic and Small Biotech Perspective  
Frank Longo, MD, PhD—Stanford University & PharmatrophiX |
| 2:05–2:15 | Q&A                                                                   |
| 2:15–2:35 | Finding and Working with Industrial Partners                        
Diana Wetmore, PhD—Harrington Discovery Institute |
| 2:35–2:45 | Q&A                                                                   |
| 2:45–3:00 | Closing Remarks                                                       
Howard Fillit, MD—Alzheimer’s Drug Discovery Foundation |
Funding for this conference was made possible, in part by Cooperative Agreement 1U13AG052268-01 from the National Institute on Aging.

The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention by trade names, commercial practices, or organizations imply endorsement by the U.S. Government.
Congratulations to all of the 2017 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.

OUTSTANDING YOUNG INVESTIGATOR AWARDS

Simone Crivelli, MS, Maastricht University
Justyna Dobrowolska Zakaria, PhD, Northwestern University
Hélène Hall, PhD, McGill University
Karolina Janczura, PhD (cand.), University of Miami Miller School of Medicine
Ryan Vest, PhD (cand.), Stanford University

YOUNG INVESTIGATOR SCHOLARSHIPS

Sweilem Al Rihani, PhD (cand.), University of Louisiana at Monroe
Sarah Caughlin, PhD (cand.), The University of Western Ontario
Kevin Doty, PhD, University of Southern California Keck School of Medicine
Sarah Gourmaud, PhD, Perelman School of Medicine at the University of Pennsylvania
Ezgi Hacisuleyman, PhD, MS, University of California, San Francisco
Anahita Hamidi, PhD (cand.), University of California, Davis
Ruyi Huang, PhD (cand.), University of California, Los Angeles
Kwok Im, University of Southern California Keck School of Medicine
Alexander Levit, MD, PhD (cand.), University of Western Ontario; Schulich School of Medicine & Dentistry
Denglei Ma, PhD (cand.), New York State Institute for Basic Research
Korrie Mack, PhD (cand.), Perelman School of Medicine at the University of Pennsylvania
Zahra Manji, Emory University School of Medicine
Jasmina Markulin, PhD (cand.), St Vincent’s Institute of Medical Research
Youssef Mousa, PhD (cand.), University of Louisiana at Monroe
Kelsey Murphy, PhD (cand.), University of Toledo
Killian Oukoloff, PhD, University of California, San Diego
Mekala Raman, PhD, Boston University
Cory Richman, MS, McMaster University
Krista Spiller, PhD, University of Pennsylvania
Elliot Swartz, University of California, Los Angeles
Andy Tay, PhD (cand.), University of California, Los Angeles*
Emelyne Teo, PhD (cand.), National University of Singapore*
Ana Viegas, PhD (cand.), Center for Neuroscience and Cell Biology
Yunze Wen, MD, Weill Cornell Medicine in Qatar
Emma Wu, University of California, San Diego

*Not in attendance
CHAIRS AND SPEAKERS

BIOS AND ABSTRACTS
DAY 1: Welcome Remarks

Howard Fillit, MD, Alzheimer’s Drug Discovery Foundation

Dr. Howard Fillit is an internationally recognized physician-scientist (a geriatrician and neuroscientist) and non-profit executive. He is a leading expert in Alzheimer’s disease with extensive experience in academia, philanthropy and industry.

Dr. Fillit is the founding Executive Director and member of the Board of Directors of the Institute for the Study of Aging (ISOA), a private foundation established by Leonard and Ronald Lauder in 1998.

Since 2004, he has also been the Founding Executive Director and Chief Science Officer of the Alzheimer’s Drug Discovery Foundation (ADDF), a public charity and affiliate of ISOA. ISOA and ADDF are dedicated to accelerating drug discovery and development for Alzheimer’s disease. Since 1998, these organizations have provided over $103MM to over 564 academic and biotechnology drug discovery and development programs in 18 countries.

Dr. Fillit currently holds the title of clinical professor of geriatrics and palliative medicine, medicine, and neuroscience at The Icahn School of Medicine at Mount Sinai (NY). He is also a Physician at The Rockefeller University Hospital. He received his BA in neurobiology cum laude from Cornell University, and his MD from the SUNY-Upstate Medical University.

From 1995-1998, Dr. Fillit was the Corporate Medical Director for Medicare at NYLCare Health Plans (one of the largest national managed care organizations in the US at the time, a division of New York Life acquired by Aetna), providing leadership for program and policy in the provision of managed care to over 125,000 elderly individuals in several regional US markets.

Dr. Fillit has served as a member of the Board of Directors for several biotechnology companies, and has been a consultant to, member, or Chair of Scientific and Clinical Advisory Boards for numerous pharmaceutical, biotechnology and health care companies.
Dr. Jacob Hooker career exemplifies the potential of discovery in chemistry to have profound impact on human health and wellbeing. Through the development of new tools and techniques, Prof. Hooker is advancing our fundamental understanding of diseases and disorders like Alzheimer’s and autism.

Dr. Hooker’s work has led to many landmark firsts—first human neuroepigenetic imaging technology, first linkage between glial activation and chronic low back pain, first demonstration of dynamic neurochemical imaging (fPET)—and catalyzes others to achieve advances of their own. He has dramatically expanded the capabilities of PET imaging by pioneering new radiotracer synthesis methods. He founded and directs a first-in-class imaging facility that merges functional MRI and positron emission tomography for neurochemical study.

Dr. Hooker’s dedication to advancing chemistry to understand and intervene in disease was demonstrated recently with the publication of the first images of epigenetic activity in the live human brain. In this innovation as in his many others, Dr. Hooker has invented—and applied—technologies that will improve medicine. Still early in his career, his peers and mentors recognize his ability to ask, and answer, compelling questions that will have lasting importance.

Developing Radiotracers to Assess Target Engagement and Beyond in the Brain

Jacob Hooker

Martinos Center for Biomedical Imaging, Massachusetts General Hospital Department of Radiology, Harvard Medical School, Charlestown, MA, USA

There are an estimated 5.4 million Americans living with Alzheimer’s disease. Over 4% of all adults have suffered from a serious mental illness in the past year. An enormous failure rate in clinical trials has resulted in few to no effective treatments for these neurological diseases, necessitating a dramatic improvement in our understanding of the human neurobiology and neurochemistry that leads to disease. The challenge is daunting given our incredibly limited ability to monitor the molecular dynamics in the living human brain at rest, during stimulation, or through drug manipulation. New hybrid, non-invasive imaging cameras can now provide the first glimpse of both chemical changes resulting from disease phenotypes or drug treatment (target engagement) in the brain and the functional changes that result. What’s more is that these simultaneous imaging systems enable us to explore the interplay between two (or more!) neurotransmitter systems and the functional consequence they facilitate in the brain. These changes can be resolved temporally and taken together can provide the basis for the first whole-brain neurochemical models.

My presentation will review human imaging technologies that can be used to understand neurochemistry and accelerate drug discovery. Using examples from my research group, I will describe the signatures of neuroinflammation that exist in neurodegeneration, consider emerging opportunities for neuroepigenetic imaging, and highlight new technologies that we are developing that are poised to fundamentally change what we can measure in the living human brain.
DAY 2: Opportunities for Translational Research Funding

Lauren Friedman, PhD, Alzheimer’s Drug Discovery Foundation

Lauren Friedman, PhD, is the Associate Director of Scientific Programs at the Alzheimer’s Drug Discovery Foundation (ADDF) where she supports the management of the ADDF’s drug discovery portfolio by providing scientific and strategic review of preclinical drug discovery proposals and tracking program progress.

Additionally, she manages the ADDF ACCESS program, which provides a virtual network of contract research organizations (CRO) and consultants, and offers educational resources on drug discovery and CRO selection and management. 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 the 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.

ADDF Funding Opportunities

Lauren Friedman

Alzheimer’s Drug Discovery Foundation, New York, NY, USA

Dr. Friedman will present Alzheimer’s Drug Discovery Foundation’s spectrum of funding opportunities and programs.

Lorenzo Refolo, PhD, National Institute on Aging

Dr. Lorenzo Refolo is the Director for Alzheimer’s Disease Drug Discovery and Development at the National Institute on Aging (NIA). He received his Ph.D. in Molecular Genetics from the Rutgers University School of Medicine and, postdoctoral training at the Laboratory of Neurobiology at Rockefeller University and, Department of Psychiatry at Mount Sinai School of Medicine. Following his postdoctoral training, Dr. Refolo held positions as Assistant Professor at Mount Sinai School of Medicine, New York, Associate Consultant and Assistant Professor at the Mayo Clinic, Jacksonville, Florida and, Research Scientist at the Nathan Kline Institute for Psychiatric Research at New York University. After leaving academia Dr. Refolo was the Scientific Director at the Institute for the Study of Aging where he created and managed a large portfolio of Alzheimer’s drug discovery programs. In 2005 Dr. Refolo joined the NIH as a Program Director at the National Institute of Neurological Disorders and Stroke (NINDS), managing a portfolio of basic, clinical, and translational research that was focused on neurodegenerative diseases. He has been at the NIA since 2010, and has developed and managed a diverse portfolio of translational research programs.

Bridging the Preclinical to Clinical Gap: An Overview of Translational Research Programs at the NIA

Lorenzo Refolo

National Institute on Aging, Bethesda, MD, USA

The talk will provide an overview of the NIA Translational Research Program and focus on a number of funding opportunities and initiatives available to investigators.
Amir Tamiz, PhD, National Institute for Neurological Diseases and Stroke

Dr. Amir Tamiz is a Program Director at the National Institute of Neurological Disorders and Stroke (NINDS), Office of Translational Research (OTR). In this capacity, Dr. Tamiz oversees NIH Blueprint Neurotherapeutics network (BPN) and Innovation Grants to Nurture Initial Translational Efforts (IGNITE).

Prior to joining NIH in 2012, Dr. Tamiz had held scientific and management positions in research and development of therapeutic programs at Corvas International (acquired by Dendreon), CovX (now part of Pfizer), and Alba Therapeutics.

Dr. Tamiz received his PhD at University of Oregon and conducted postdoctoral research at the Department of Neuroscience at Georgetown University Medical Center.

NINDS Opportunities for Translational Research Funding

Amir Tamiz

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

The Division of Translational Research (DTR) at the National Institute of Neurological Disorders and Stroke (NINDS) provides many funding opportunities to accelerate leading-edge preclinical research.

DTR helps academic and industry researchers create a bridge through which discoveries made in the lab lead to new and improved medical treatments and options for patient care.

DTR provides funding and resources (approximately $100 million annually) through grants, cooperative agreements, and contracts to academic and industry researchers to advance early-stage neurological technologies, devices, and therapeutic programs to industry adoption (i.e., investor funding and corporate partnerships).

DTR comprises of six programs that support the design, implementation, and management of research activities to critical translational challenges in neurology.

The presentation will cover funding opportunities at DTR/NINDS and provide examples for best practices for converting basic research discoveries into therapeutic modalities for treatment of neurological disorders and stroke.
SESSION I: Embarking on a Drug Discovery Campaign

Chair: Marcie Glicksman, PhD—Orig3n, Inc.

What Makes a Good Target: A Perspective in Neurodegenerative Disease Therapeutic Discovery
Samuel Hasson, PhD—Pfizer, Neuroscience Unit

New Trends and Technology in Assay Development
Marcie Glicksman, PhD—Orig3n, Inc.

Development of Small-Molecule Autophagy Inducers that Mitigate Neurodegeneration
Steven Finkbeiner, MD, PhD—Gladstone Institute of Neurological Disease
SESSION I: Embarking on a Drug Discovery Campaign

Samuel Hasson, PhD, Pfizer, Neuroscience Unit

Dr. Samuel Hasson is a Principal Investigator and Lab Head in Pfizer Neuroscience (Cambridge, Massachusetts).

His lab focuses on the discovery of novel therapeutic avenues in neurodegenerative disease that are rooted in human biology and genetics. A major goal of his work is to identify modulators of complex phenotypes in areas such as neuroinflammation and mitochondrial health by utilizing innovative assay design and screening strategies.

As aging is a key risk factor for neurodegenerative disease, Dr. Hasson’s training in mitochondrial biology and quality control as a graduate student (UCLA) and postdoc (NIH) help guide his current research.

What Makes a Good Target? A Perspective in Neurodegenerative Disease Therapeutic Discovery

Samuel Hasson

Pfizer, Neuroscience Unit, Cambridge, MA, USA

The discovery of therapeutic agents is a constantly evolving science, impacted by a combination of technological innovation, methodological ideology, and shifts in the understanding of human disease. A common theme in drug discovery is the idea of a drug target as a focal point in the efforts to treat underlying pathology or emergent symptoms. Classically, drug targets have emerged from knowledge of specific cellular pathways driving illness and also from the application of novel pharmacology, often serendipitously, in disease models. Given the challenge of developing therapies for the CNS, a modern take on the selection of drug targets involves the range of intervention strategies available today. Additionally, due to translational challenges in studying human diseases in rodents, a new emphasis is placed on human biology and genetics in the selection of therapeutic hypotheses.
Dr. Marcie Glicksman is the Chief Scientific Officer at Orig3n, Inc., a biotechnology company that has established the world’s largest uniformly consented HLA-matched cell repository to be used to better understand the cellular and molecular foundations of disease.

Dr. Glicksman has been in the field of drug discovery for more than 20 years. Previously, Dr. Glicksman was the Co-Director of the Laboratory for Drug Discovery in Neurodegeneration (LDDN), which aimed at accelerating the identification of new therapeutics. While at LDDN, she helped start eight new companies, one that now has a commercial product.

Previously, she was at Descartes Therapeutics which focused on pain therapeutics and then, at Cubist, which targeted novel antibiotics. Prior to these positions, she was at DuPont-Merck and at Cephalon, Inc. Dr. Glicksman has led multiple advanced programs for neurodegenerative diseases including co-inventorship of CEP1347, a drug candidate directed at a kinase that has been in Phase III clinical trials. She has also been part of the team to prepare an IND for a drug for neuropathic pain that has just completed Phase II clinical trials.

From 2005-2009, Dr. Glicksman was elected to the Board of Directors and served as Chairman of the Board for the Society for Biomolecular Sciences (now Society for Laboratory Automation and Screening). Dr. Glicksman is also on the Science Advisory Board for the Alzheimer’s Drug Discovery Foundation (ADDF), the California Institute for Regenerative Medicine (CIRM), and reviews grants for NIH, Department of Defense, SBIR, the Michael J Fox, Alzheimer’s Association, and Rett Foundation.

Dr. Glicksman co-founded the Academic Drug Discovery Consortium as a way to build a collaborative network for the academic drug discovery community. She co-designed and developed an annual drug discovery course supported by NIH. 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 in Neuroscience from Washington University. She has over 75 publications and 16 issued patents.

New Trends and Technology in Assay Development

Marcie Glicksman

Orig3n, Inc., Boston, MA, USA

Neurodegenerative diseases are challenging from a drug discovery perspective with no disease modifying agents available on the market. The lack of success is at least partly due to the poor disease models that have been available for a biologically complex system as the brain. Much of the success in drug discovery is dependent on assay development strategies.

My presentation will highlight choices needed to be made in selecting the best assay based on your target. I will also discuss new assay development trends, for example, the pros and cons for target-based versus phenotypic-based assays, the role of patient-derived induced pluripotent stem cells and primary cells and other technologies that are available for creating better disease models.
SESSION I: Embarking on a Drug Discovery Campaign

Steven Finkbeiner, MD, PhD, Gladstone Institute of Neurological Disease

Dr. Steven Finkbeiner is the Director of the Taube/Koret Center for Neurodegenerative Disease Research at The J. David Gladstone Institutes. The Taube/Koret Center is a philanthropy-supported entity, which was established in 2009 to accelerate the development of drug therapies for patients suffering from conditions such as Huntington’s disease. He is best known for his pioneering work on neurodegenerative diseases. He invented robotic microscopy, a new form of imaging that has helped unravel cause-and-effect relationships in amyotrophic lateral sclerosis (ALS, or Lou Gehrig’s disease), Huntington’s, Alzheimer’s and other neurodegenerative diseases. Dr. Finkbeiner used his robotic microscope to resolve a long-standing puzzle in Huntington’s disease. A study based on results from the microscope became the most-cited paper in the field of neuroscience in the last decade.

Dr. Finkbeiner has received numerous awards for his work, including the Lieberman Award, the Taube/Koret Prize and the Award for Outstanding Research Achievement from Nature Biotechnology, and was elected to the American Neurological Association in 2014.

Dr. Finkbeiner is also a Professor of Neurology and Physiology at the University of California, San Francisco and is active in graduate training as a member of the Neuroscience, Biomedical Sciences and Medical Scientist Training Programs at the University. He also serves as an associate editor for Autophagy, and is on the editorial board of the Journal of Huntington’s Disease and Molecular Neuropsychiatry.

In 1986, Dr. Finkbeiner earned a bachelor’s degree from Wheaton College. He earned both an MD and a PhD in neuroscience from Yale University in 1991. He completed an internship in internal medicine and chief residency in neurology at the University of California, San Francisco, followed by a research fellowship at Harvard Medical School.

Development of Small-Molecule Autophagy Inducers that Mitigate Neurodegeneration

Steven Finkbeiner

Taube/Koret Center for Neurodegenerative Diseases, Gladstone Institutes and UCSF, San Francisco, CA, USA

The abnormal accumulation of misfolded proteins in the brains of patients who suffer from Alzheimer’s disease (AD), Parkinson’s disease (PD), frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS) and Huntington’s disease indicates a fundamental mismatch in the production and clearance of misfolded proteins. The observation that mutations in many genes encoding components of the autophagy/lysosome protein clearance pathway give rise to a variety of neurodegenerative diseases further implicates protein dyshomeostasis as an important disease mechanism. Autophagy is one of the two major protein clearance pathways in cells and the only pathway thought to be capable of clearing accumulated toxic misfolded proteins. We hypothesized that stimulating the endogenous autophagy pathway in brain cells could be a therapeutic strategy for treating disorders characterized by protein misfolding and accumulation. We conducted a candidate screen and identified small molecules that induce autophagy in neurons. Using computational chemistry and the initial structure-activity relationships, we developed a pharmacophore and performed in silico screening of a 1M compound library and identified additional small-molecule autophagy inducers that were more potent and had a wider therapeutic window. One of the major challenges of developing autophagy inducers is that many of the conventional assays are slow and insensitive, relying on snap-shot measures of autophagy pathway intermediates to infer flux through the pathway. To overcome this limitation, we developed a new optical pulse-labeling method to directly measure flux through the autophagy pathway, and we adapted it to a high-throughput walkaway robotic microscopy platform. With this platform and medicinal chemistry approaches, we developed potent (nanomolar) compounds with novel chemistry that stimulate autophagy in rodent and human neurons in vitro and in vivo and are protective in rodent and human neuron models of ALS and other neurodegenerative disorders. The molecules have drug-like properties, are orally bioavailable, have excellent blood-brain barrier penetration, and appear to be safe with chronic dosing. We are continuing to develop these molecules with the goal of choosing a clinical candidate for first-in-human trials.
SESSION II: Starting at the End: The Pharmacology—Chemistry Interface in Preclinical Drug Development

Chair: D. Martin Watterson, PhD—Northwestern University

Medicinal Chemistry for Today's Biology
Dario Doller, PhD—Alcyoneus/ScienceWorks

Fragment-based Drug Discovery
Daniel Erlanson, PhD—Carmot Therapeutics, Inc.

Pharmacology Driven Optimization in Candidate Development
D. Martin Watterson, PhD—Northwestern University
SESSION II: Starting at the End: The Pharmacology—Chemistry Interface in Preclinical Drug Development

Dario Doller, PhD, Alcyoneus/ScienceWorks

Dr. Dario Doller is currently Senior Director, Deuterium Platform, at Concert Pharmaceuticals, exploiting the potential of deuteration in drug discovery. In his spare time, Dario follows new developments in the areas of allosterism and systems chemistry, aiming to gain a better understanding of drug action at the molecular level, in particular for membrane-bound receptors.

Dario was born and raised in Buenos Aires, Argentina, where he earned a doctorate in Chemistry at the Facultad de Ciencias Exactas, Universidad de Buenos Aires. He then conducted postdoctoral work in Bio-organic chemistry with Sir Derek Barton at the Chemistry Department, Texas A&M University. Dario has held industrial positions of increasing responsibility at Rohm & Haas, Schering-Plough Research Institute, 3-Dimensional Pharmaceuticals, Gliatech, Neurogen, Lundbeck Research USA. He consults through Alcyoneus/ScienceWorks.

During his career, Dario has uncovered reaction mechanisms, invented novel chemical reactions, contributed as medicinal chemist to the discovery of the FDA-approved PAR-1 antagonist Vorapaxar, and helped deliver clinical compounds working at GPCRs, most notably the MCHR1 antagonist NGD-4715 and the mGluR5 NAM Lu AF09535. In addition, he has contributed to the design of radioligands and PET ligands, as well as a number of novel probe compounds for chemical biology and target validation studies.

Over the last decade, Dario lead global pre-competitive efforts to study potential therapeutic use of allosteric and orthosteric mGluR ligands. Dario has co-authored more than 100 peer-reviewed publications, patents and book chapters. He recently edited the book “Allosterism in Drug Discovery” for RSC’s Drug Discovery Series.

Medicinal Chemistry for Today’s Biology

Dario Doller

Alcyoneus/ScienceWorks, Boston, MA, USA

Society expects that the wave of contemporary new discoveries in biological sciences will soon lead to novel treatments for human diseases, including many devastating brain disorders. Historically, medicinal chemists have contributed to drug discovery teams in ways that synergize with those from their partner sciences, and help transform new knowledge into the ultimate tangible asset: a new drug.

Medicinal chemists in drug discovery project teams are responsible for a variety of tasks. These include, among others: the synthesis of compounds for testing of a design hypothesis, developing structure-activity and structure-property relationships, and most importantly for novel biological targets, help establish the desired target product profile for the drug candidate.

Medicinal chemists work using diverse strategies, which are tailored to the specific profile sought in a compound. We exemplify some of these strategies by discussing the importance of compound purity, membrane permeability, brain penetration.
SESSION II: Starting at the End: The Pharmacology—Chemistry Interface in Preclinical Drug Development

Daniel Erlanson, PhD, Carmot Therapeutics, Inc.

Dr. Daniel Erlanson is the co-founder of Carmot Therapeutics, Inc. (http://www.carmot.us).

Using a proprietary technology called Chemotype Evolution, Carmot is addressing unmet chemical needs in drug discovery to tackle challenging therapeutic targets.

Prior to Carmot, Dr. Erlanson spent a decade developing technologies and leading medicinal chemistry efforts in oncology and in metabolic and inflammatory diseases at Sunesis Pharmaceuticals, which he joined at the company’s inception. Before Sunesis, he was an NIH postdoctoral fellow with James A. Wells at Genentech.

Dr. Erlanson earned his PhD in chemistry from Harvard University in the laboratory of Gregory L. Verdine and his BA in chemistry from Carleton College. As well as co-editing two books on fragment-based drug discovery, Dr. Erlanson is an inventor or author on more than forty patents and scientific publications. He is also editor of a blog devoted to fragment-based drug discovery, Practical Fragments (http://practicalfragments.blogspot.com/).

Fragment-based Drug Discovery

Daniel Erlanson

Carmot Therapeutics, Inc., San Francisco, CA, USA

Faced with the need to deliver drugs and tool compounds against increasingly difficult targets, many researchers have turned to fragment-based drug discovery (FBDD) as an alternative to traditional high-throughput screening. Rather than screening millions of drug-sized compounds, fragment-based drug discovery starts with libraries of just a few thousand very small molecules, or fragments. This enables a more thorough exploration of chemical space to find better starting points for lead optimization. It also allows greater attention to physicochemical properties, which are particularly important for drugs targeting the central nervous system. More than thirty FBDD-derived drugs have entered the clinic, with two approved so far. However, because the initial fragment hits are so weak, artifacts are a serious concern if they go unrecognized.

This presentation provides an overview of FBDD and touches on what works – as well as what to avoid.
D. Martin Watterson, PhD, Northwestern University

Dr. Daniel Martin Watterson serves in an advisory role to pharmaceutical and biotechnology companies in the areas of process and risk analysis. In addition to industry consulting, Dr. Watterson serves on advisory boards for small business start-ups, biotechnology companies, and non-profit organizations in the area of CNS drug discovery and development. His personal CNS drug development experience includes the discovery and preclinical development of novel small molecule therapeutic candidates that attenuate disease related to synaptic dysfunction, as well as participation in development of protein replacement therapeutics.

Dr. Watterson is the G.D. Searle Endowed Chair Professorship at Northwestern University, where he is also Professor of Pharmacology in the Feinberg School of Medicine. Previous relevant activities at Northwestern include the founding of an academic drug discovery research and training program characterized by the generation of multiple CNS drug candidates taken into preclinical and clinical development through the leveraged use of Foundation and NIH funding. He also served in various administrative positions, including Department Chair, University Center Director, and Curriculum Co-Director.

Prior to Northwestern, he held faculty positions at The Rockefeller University, where he was an Andrew Mellon Fellow, and at Vanderbilt University Medical Center, where he was Professor of Pharmacology and an Investigator in the Howard Hughes Medical Institute. Dr. Watterson is the recipient of the 2016 Melvin R. Goodes Prize recognizing researchers working in promising areas of drug discovery for Alzheimer’s disease and related dementias.

Pharmacology Driven Optimization in Candidate Development

Daniel Martin Watterson

Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

A theme in this session is how “smart chemistry” can be used as an overarching strategy for novel small molecule drug candidates targeting CNS disorders and contribute to risk reduction at the first-in-human and first-in-patient clinical stages. For example, a continuing risk for clinical phase 1 and phase 2 investigations is tissue exposure limited by the challenge of blood brain barrier (BBB) penetrance of the active molecular species (parent compound or metabolites). As discussed in previous presentations on medicinal chemistry driven risk reduction, a common risk reduction theme across diverse chemotypes, drug target classes and CNS disease indications is consideration of multi-property optimization (MPO) during synthetic design and ADMET driven refinement. MPO considerations focus on a nexus of molecular properties such as lipophilicity (log P), surface charge (PSA) and size (MW) that are correlated with partitioning for BBB penetrance. These same MPO features overlap the inherent risk in P450 (CYP) mediated first pass metabolism, such as generating a CYP2D6 substrate which raises the potential for individual variability in efficacy or toxicity. A subset of molecular properties are also associated with risk of substrate status for efflux pumps. Overall, a primary strategic approach to most CNS drug discovery and campaigns is the use of such “smart chemistry” considerations.

“Smart biology”, the use of pharmacology driven screens, is now used in an integrated fashion with “smart chemistry”. The overall approach is one of hierarchal screens to obtain outcomes that drive the recursive phase of “smart chemistry”. The early stage tactic is one of keep-it-simple. A series of in vitro and in vivo pharmacological screens are employed in a hierarchal and recursive paradigm that facilitates rank ordering of initial novel compounds. The outcomes can be used as a driver of medicinal chemistry refinement. Commercial availability of key reagents and cost-effective CRO with standardized experimental protocols has greatly facilitated this recent trend. Generally, the approach allows for fewer total syntheses and a rapid identification of pharmacological “hot spots” in second generation compounds. The intermediate goal is to parse, or kill, compounds as soon as possible. The in vivo pharmacological and pharmacodynamic screens are kept as simplified as possible. The screens are not a substitute for later stage GLP safety analyses or efficacy investigations. The keep-it-simple tactic views the particular screen choice as a surrogate for a later stage investigation that has significant risk potential. The approach, thereby, reduces accumulated cost and effort by pushing risk reduction to an earlier stage while the program is under the medicinal chemistry umbrella. This presentation will be brief set of examples to demonstrate how the strategy can be applied to a project specific tactical approach.
SESSION III: Drug Discovery: From Lead to Clinical Candidate

Chair: Edward Spack, PhD—Vector BioSolutions

PK/PD in Preclinical Development
Sharon Rosenzweig-Lipson, PhD—AgeneBio, Inc.

Alternative Animal Models for In Vivo Efficacy and Study Design Considerations
Joseph Araujo—InterVivo Solutions, Inc.

Drug Delivery for CNS
Ruben Boado, PhD—ArmaGen, Inc.

Requirements for an IND
Edward Spack, PhD—Vector BioSolutions

Young Investigator Scholarship Awards Presentation
Andrew Koemeter-Cox, PhD—Alzheimer’s Drug Discovery Foundation
SESSION III: Drug Discovery — From Lead to Clinical Candidate

Sharon Rosenzweig-Lipson, PhD, AgeneBio, Inc.

Dr. Sharon Rosenzweig-Lipson, is President of IVS Pharma Consulting. In 2011, Dr. Rosenzweig-Lipson founded IVS Pharma Consulting to bring her expertise in screening strategies, in vivo models, translation and early clinical development strategy to the neuroscience scientific community in pharma, biotech and academia.

She has over 20 years’ experience developing compounds for psychiatric and neurologic indications in the pharmaceutical industry. She has successfully led teams from the earliest exploratory studies through to Phase II Proof of Concept Trials.

Prior to her current positions, Dr. Rosenzweig-Lipson held the roles of Head of Translational Neuroscience and In-Vivo Head of Psychiatry at Wyeth Research.

Dr. Rosenzweig-Lipson received her BA in Biological Basis of Behavior from the University of Pennsylvania and her PhD in Behavioral Neuroscience from Harvard University.

PK/PD in Preclinical Development

Sharon Rosenzweig-Lipson

AgeneBio, Inc., East Brunswick, NJ, USA

Pharmacokinetics is the evaluation of how the body Absorbs, Distributes, Metabolizes and Eliminates (ADME) a compound in plasma (and in CSF or brain for CNS indications). Pharmacodynamics is the evaluation of how a compound engages its target and produces the desired action (e.g. produces behavioral effect indicative of therapeutic benefit). In drug discovery, it is critical to understand the PK/PD relationship of a compound to ensure that the compound is dosed in the right amount, at the right time, by the right route of administration to ensure the compound gets to its target at sufficient exposures to produce the desired outcome. Once this exposure relationship is established, a therapeutic index for the exposures of adverse events relative to the exposure of the therapeutic effect can be determined ensuring that a compound is safe to administer to patients.

This talk will discuss in vitro predictors of in vivo pharmacokinetics. Examples from preclinical and clinical programs in AD will be used to highlight how these properties influence decision making in drug discovery.
Joseph Araujo, InterVivo Solutions, Inc.

Joseph Araujo is InterVivo Solution’s President and CEO. He is focused on optimizing the translational value of InterVivo’s services to facilitate the development and approval of novel drugs. Mr. Araujo continues to be closely involved in projects utilizing, characterizing and developing the aged dog as a natural model of age-related human diseases. Mr. Araujo is a strong proponent for the use of validated natural and/or translational animal models in drug discovery.

His scientific background includes graduate training in pharmacology at the University of Toronto, more than 25 refereed publications and several invited presentations, which exemplifies his continued passion for scientific innovation, and expertise in natural aged canine models of human disease.

Mr. Araujo directly supports developing of local biotech talent and companies and has co-founded and held executive level positions in several Ontario-based Contract Research and Life Science companies helping to build their global presence and success.

Alternative Animal Models for In Vivo Efficacy and Study Design Considerations

Joseph Araujo

InterVivo Solutions, Inc., Toronto, ON, Canada

One factor attributed to the significant number of failed clinical trials testing central nervous system (CNS) disease therapeutics is the poor predictive validity of animal models. The majority of CNS animal models rely on chemical, surgical or transgenic manipulation to model specific aspects of the relevant human disease. While these models have helped identify novel disease targets, they are limited, by design, to serve only as target engagement models for preclinical evaluation of therapeutics. Given the multi-factorial etiology and biological complexity of human diseases, translational evaluation of therapeutics for predicting clinical success should incorporate animal models that spontaneously demonstrate multiple behavioral, neuropathological and biomarker correlates of the relevant human disease, such as those seen in aged dogs and/or non-human primates.

For example, aged dogs demonstrate deficits in short-term memory and executive function associated with amyloid plaque deposition, cortical atrophy, and cholinergic deficits as well as clinically relevant biomarker changes, such as decreased CSF amyloid-beta42, reduced cerebral metabolism measured by FDG-PET, and progressive cortical atrophy, consistent with that seen in Alzheimer’s disease. Moreover, aged dog studies have predicted both positive and negative human clinical trial results.

In addition to selection of appropriate animal models, animal study designs should consider: appropriate controls (positive and negative); sufficient subject numbers (determined using power analyses); controlled environmental conditions; inclusion/exclusion criterion; blinding procedures; balanced group approaches; and incorporation of PK and PD (i.e. biomarker) data. Ultimately, a top-down approach should be employed in which a decisive animal efficacy study is designed to mirror and inform anticipated human clinical trials; likely employing a longitudinal study incorporating all relevant clinical endpoints. This approach should establish what gaps exist in the study design that can then inform designs of earlier exploratory studies such as PK-ADME and observational/PD studies. Ultimately, a pragmatic approach that accounts for animal model limitations can potentially improve ability to predict clinical success.
SESSION III: Drug Discovery — From Lead to Clinical Candidate

Ruben Boado, PhD, ArmaGen, Inc.

Dr. Boado co-founded ArmaGen in 2004, following more than 25 years of academic experience in fields of molecular and cell biology of the BBB, and drug delivery to the brain. His leadership and expertise have been instrumental in the development of ArmaGen’s extensive product pipeline, including potential biotherapeutic treatments for mucopolysaccharidosis, stroke, Alzheimer’s disease and Parkinson’s disease.

Dr. Boado was the principal investigator in a number of Small Business Innovation Research (SBIR) programs granted by the National Institutes of Health to ArmaGen. Dr. Boado is also a co-inventor of the intellectual property that supports ArmaGen’s pipeline. He is Professor Emeritus of Medicine at UCLA, and has published over 200 scientific peer-reviewed publications and book chapters in his research field.

Drug Delivery for CNS

Ruben Boado

ArmaGen, Inc., Calabasas, CA, USA

Monoclonal antibodies are large molecule biotherapeutics that do not cross the blood-brain barrier (BBB). The BBB-penetration of monoclonal antibody therapeutics is enabled by re-engineering as bi-functional IgG fusion proteins. The IgG domain targets a specific endogenous receptor-mediated transporter system within the BBB, such as the human insulin receptor (HIR), to induce receptor-mediated transcytosis across the BBB. The monoclonal antibody therapeutic domain is fused to the transport IgG as a single chain variable fragment (ScFv) to exert its pharmacological effect in brain once across the BBB. Several bi-functional IgG-fusion proteins have been engineered and reduced to practice in animal models, including Alzheimer’s transgenic mice. First in human clinical trials for the CNS treatment of lysosomal storage disorders with IgG fusion proteins are in progress.
Edward Spack, PhD, Vector BioSolutions

Dr. Edward (Ted) Spack is Principal of Vector BioSolutions, a preclinical consulting and grant advising service, as well as an Innovation Partner for SRI International, advising academic and biotech start-ups around the world.

Dr. Spack has extensive translational experience, including 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, drafting preclinical development blueprints that led to several major grants and spin out companies. He has consulted with the NIH translational core services committee and several NIH institutes on preclinical development and serves on several study sections, including the NIA Alzheimer’s Disease Drug Development review panel, the NIH/CSR Drug Discovery for the Nervous System and Molecular Probes review panels, and the Falk Trust Catalyst and Transformational Award programs. Through the California Life Sciences Institute (CLSI) FAST program and the SRI Innovation program he mentors SF Bay area and international academic and industry teams in biotech company formation and pitch decks.

Dr. Edward Spack received his doctoral degree from The Johns Hopkins University and his postdoctoral fellowship in cellular immunology at Stanford University. He has worked in San Francisco Bay area biotech companies and private research institutes for over 25 years focusing on the transition from discovery to clinical trial.

Requirements for an IND

Edward Spack

Vector BioSolutions, San Francisco, CA, USA

When developing a new drug candidate or repurposing a current drug, it is wise to remember the adage: “Begin with the end in mind”. The purpose of this presentation is to provide an overview of the preclinical activities required to prepare a drug candidate for clinical testing. Understanding this path and planning the proper studies at the earliest stages of drug lead optimization increases the probability of success. In the United States, permission to initiate a clinical trial requires submission of an Investigational New Drug (IND) application to the Food & Drug Administration (FDA). 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: 1.) animal pharmacology and toxicology studies; 2.) chemistry and manufacturing processes; 3.) clinical protocol and investigator information. Previous talks will cover studies of pharmacokinetics (PK), and 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). Several useful tools and resources will be discussed, including FDA Guidance for Industry publications and other regulatory information. 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, defining optimal and minimal characteristics that will help the development team begin with the end in mind and build toward an acceptable goal. In summary, this talk will provide a basic guide to navigating the sea of three letter acronyms (CMC, COA, TOX, GLP, GMP, TPP, CFR, ICH, etc.) required for successful submission of an IND to the FDA.
ADDf Young Investigator Scholarship and Awards Presentation

Andrew Koemeter-Cox, PhD, Alzheimer’s Drug Discovery Foundation

Andrew Koemeter-Cox, PhD, works on the ADDF’s scientific initiatives, including the ACCESS program. In this capacity, he assists with reviews of funding proposals and manages the ACCESS website, which connects researchers with CROs and other drug discovery expertise.

Dr. Koemeter-Cox was most recently a postdoctoral fellow at the Icahn School of Medicine at Mount Sinai, where he studied the epigenetics of axon regeneration in the context of spinal cord injury. From 2007 until 2009, he was a research technician with the United States Army Medical Research Institute of Chemical Defense (USAMRICD), assisting with studies on neuroprotection strategies.

Dr. Koemeter-Cox earned a doctorate in biomedical science from The Ohio State University College of Medicine and a bachelor’s degree in biochemistry from the University of Delaware. He is a member of the New York Academy of Sciences, where he serves as a mentor for several programs.

DAY 3: Welcome Remarks

Diana Shineman, PhD, Alzheimer’s Drug Discovery Foundation

Dr. Diana Shineman, is the Senior 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

Jeffery Kelly, PhD, The Scripps Research Institute

Dr. Jeffery Kelly is the Lita Annenberg Hazen Professor of Chemistry in the Department of Chemistry and the Chairman of the Department of Molecular Medicine at the Scripps Research Institute.

Dr. Kelly also served as Vice President of Academic Affairs and Dean of Graduate Studies at Scripps for nearly a decade. His research is focused on uncovering protein folding principles and on understanding the etiology of protein misfolding and/or aggregation diseases and using this information to develop novel therapeutic strategies. He has 320+ publications (h-index > 85), has been elected to the American Academy of Arts and Sciences (2016) and has received several awards, the most recent being the Jacob and Louise Gabbay Award in Biotechnology and Medicine (2016) and The Royal Society of Chemistry Jeremy Knowles Award (2016).

Dr. Kelly cofounded FoldRx Pharmaceuticals based on his discovery of Tafamidis, approved by several regulatory agencies to treat familial amyloid polyneuropathy, and now sold by Pfizer. He also cofounded Proteostasis Therapeutics, a public company, developing drugs for Cystic Fibrosis and other proteinopathies.

Dr. Kelly serves on the board of directors of several public and private companies.

Adapting the Chemistry and/or Biology of Proteostasis to Ameliorate Protein Aggregation Diseases

Jeffery Kelly

The Skaggs Institute of Chemical Biology, The Scripps Research Institute, La Jolla, CA, USA

The cellular protein homeostasis, or proteostasis network, regulates proteome function by controlling ribosomal protein synthesis, chaperone and chaperonin mediated protein folding, protein trafficking, protein degradation and related processes. Stress responsive signaling pathways match proteostasis network capacity with demand in each subcellular compartment to maintain or alter cellular homeostasis. The beginning of the seminar will focus on how the proteostasis network can be adapted through unfolded protein response arm-selective signaling to alleviate gain-of-toxic-function diseases where excessive secretion of misfolding and aggregation of proteins leads to an amyloid disease. I will explain how distinct arms of the unfolded protein response can be activated to reduce transthyretin secretion, which in turn reduces amyloidogenesis or aggregation. The audience will next be updated on the progress made to date to develop small molecule, arm-selective UPR activators, that are envisioned to be useful for cancer treatment or gain-of-proteotoxicity diseases. This part of the seminar will focus on a pharmacologic strategy to adapt protein homeostasis by activating the ATF6 pathway to alleviate Light chain amyloidosis—a plasma cell cancer with a proteotoxicity component. We have developed and characterized drug candidates that block light chain secretion and aggregation, and some of these also kill the plasma cancer cells by a mechanism we are starting to understand. Lastly, chemical approaches to restore proteostasis will be exemplified. High affinity small molecule binding to the normally folded structural ensemble of an aggregation-prone protein inside and/or outside of the cell stabilizes its native state, lowering the population of misfolded, misassembly competent states that lead to aggregates, including amyloid fibrils. Therefore, crafting small molecules that selectively bind to the normally folded conformational ensemble of an aggregation-prone protein is a promising strategy to treat human amyloid diseases. I will focus on outlining this approach to ameliorate the transthyretin (TTR) amyloidoses; demonstrating that preferential ligand binding to and stabilization of the native tetrameric state of TTR over the dissociative transition state dramatically raises the kinetic barrier of dissociation (rate-limiting for amyloidogenesis), slowing, and in many cases halting the process of TTR amyloid fibril formation. Recently, we showed that Tafamidis or Vyndaqel, a small molecule kinetic stabilizer of Transthyretin, halts the progression of Familial Amyloid Polyneuropathy in a placebo controlled clinical trial of 18-month duration, featuring an 18-month follow-on study, according to several clinical trial metrics. There is also reason to be optimistic that Tafamidis (Vyndaqel) may ameliorate the cardiomyopathies associated with amyloidogenesis of either wild-type TTR or selected mutants. This is the first drug reported to alter the underlying etiology of a human amyloid disease. Perhaps more importantly, this study represents the first pharmacologic evidence supporting the hypothesis that the process of amyloid fibril formation causes the degeneration of post-mitotic tissue (i.e. the peripheral nervous system, the autonomous nervous system and the heart and possibly other muscles) in the human amyloidosis. In other words, the preclinical and clinical trial results strongly support the amyloid hypothesis as the basis for these diseases.
SESSION IV: Strategies for Challenging CNS Targets—Case Study Examples

Chair: Kurt Brunden, PhD—Perelman School of Medicine at the University of Pennsylvania

Intrathecal Stem Cell Therapy for Multiple Sclerosis
Violaine Harris, PhD—Tisch Multiple Sclerosis Research Center of New York

Academic-Industry Partnerships: Potential Benefits and Pitfalls with a Case Example
Kurt Brunden, PhD—Perelman School of Medicine at the University of Pennsylvania

Preparing for an IND: Case Study in the Development of a Small Molecule for a Neurodegenerative Disorder
Douglas Bonhaus, PhD—Neuropore Therapies

Antisense Oligonucleotides for The Treatment of Huntington’s Disease: Lessons Learned from Mice and Non-Human Primates
Hien Tran Zhao, PhD—Ionis Pharmaceuticals, Inc.

Repurposing Drugs for Neurodegenerative Diseases
Albert La Spada, MD, PhD—University of California, San Diego School of Medicine
SESSION IV: Strategies for Challenging CNS Targets—Case Study Examples

Violaine Harris, PhD, Tisch Multiple Sclerosis Research Center of New York

Dr. Violaine Harris is a Senior Research Scientist at the Tisch Multiple Sclerosis Research Center of New York where she has developed cell therapy strategies to promote repair and regeneration in multiple sclerosis. Dr. Harris has had a longstanding interest in stem cell biology and in understanding the mechanisms of cell signaling and differentiation. She received her PhD in Pharmacology/Tumor Biology from Georgetown University, and she subsequently trained as a postdoctoral fellow at Mount Sinai Medical Center, where she studied mechanisms involved in the maintenance of cancer stem cells.

Stem cell research conducted by Dr. Harris over the past 10 years at the Tisch MS Research Center of New York has led to a groundbreaking Phase I clinical trial, the first to test intrathecal administration of bone marrow-derived neural progenitors in patients with MS.

She is the director of the new Cell Therapy Facility at Tisch MS, designed to manufacture clinical grade autologous stem cells for an upcoming Phase II trial. Her laboratory research continues to focus on mechanisms and biomarkers of cell-mediated repair and regeneration in the CNS.

Intrathecal Stem Cell Therapy for Multiple Sclerosis

Violaine Harris

*Tisch Multiple Sclerosis Research Center of New York, NY, USA*

Multiple sclerosis (MS) is an autoimmune-mediated demyelinating disease of the CNS associated with a progressive clinical course causing significant physical disability. MS disease progression is associated with axonal degeneration and oligodendroglial cell depletion, in addition to the hallmark demyelination. The goal of stem cell-based regenerative therapies is to halt or reverse disease progression and disability in MS. We have investigated the use of mesenchymal stem cell-neural progenitors (MSC-NPs), which represent a neural subpopulation of bone marrow MSCs. Proof-of-concept studies both in vitro and in the mouse model of MS demonstrated the therapeutic potential of intrathecally (IT) injected MSC-NPs based on their immunoregulatory and trophic properties. Recently, a Phase I clinical trial was completed in 20 subjects with progressive MS showing that repeated IT-MSC-NP administration is safe and well tolerated. Although the trial was open-label, the data demonstrated that >70% of patients showed measurable reversal of established disability as assessed by motor strength, motor function, and bladder function.

We will discuss the challenges faced in the development of IT-MSC-NP therapy, including (1) establishing robust quality testing of autologous cell products; (2) the role of pilot clinical data in determining safety and tolerability; and (3) the importance of route of administration and multiple dosing in cell-based targeting of the CNS. The successful outcomes of the IT-MSC-NP clinical trial suggest that additional clinical testing is warranted in both MS and in other neurodegenerative diseases.
SESSION IV: Strategies for Challenging CNS Targets—Case Study Examples

Kurt Brunden, PhD, Perelman School of Medicine at the University of Pennsylvania

Dr. Kurt Brunden is Director of Drug Discovery and a Research Professor in the Center for Neurodegenerative Disease Research (CNDR) at the University of Pennsylvania, where he oversees drug discovery programs in the areas of Alzheimer’s disease (AD), frontotemporal lobar degeneration and Parkinson’s disease.

Prior to joining CNDR in 2007, Dr. Brunden was an executive in the biotechnology sector, where he served as VP of Research at Gliatech, Inc. and later as Sr. VP of Drug Discovery at Athersys, Inc. In these positions, he initiated and managed drug discovery programs in AD, cognitive enhancement, schizophrenia, inflammation, metabolic disease and cancer. Prior to his time in industry, Dr. Brunden was an NIH-funded faculty member within the Biochemistry Department at the University of Mississippi Medical Center, with a research focus on the regulation of myelination.

He obtained his B.S. degree (magna cum laude) from Western Michigan University, with dual majors of Biology and Health Chemistry, and his Ph.D. in Biochemistry from Purdue University, with a post-doctoral fellowship at the Mayo Clinic. Dr. Brunden has over 100 scientific publications, and multiple issued and pending U.S. and PCT patents.

Academic-Industry Partnerships: Potential Benefits and Pitfalls with a Case Example

Kurt Brunden

Center for Neurodegenerative Disease Research, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Pharmaceutical companies are increasingly seeking partnerships with qualified academic collaborators, particularly in difficult therapeutic areas like neurodegenerative disease. Industry seeks such collaborations for multiple reasons, including a desire to expand constrained internal efforts through support of researchers who are expert in the desired therapeutic space, and/or to obtain access to novel assays or disease models. If structured properly, such partnerships can be mutually beneficial, allowing academic scientists the opportunity to translate research findings into tangible therapeutic opportunities, while providing the pharmaceutical partner with capabilities or insights that might have been difficult to obtain internally.

Our laboratory has had several research and development partnerships with the pharmaceutical sector, and the potential benefits and pitfalls of such collaborations will be discussed, as well as an example partnership in which the focus was on the identification of therapeutic antibodies for the treatment of neurodegenerative tauopathies.
Preventing an IND: Case Study in the Development of a Small Molecule for a Neurodegenerative Disorder

Douglas Bonhaus

Neuropore Therapies, San Diego, CA, USA

For many startup pharmaceutical companies or academic groups, the submission of an IND application represents a major milestone in the progression of a therapeutic concept into a clinically evaluated drug-candidate. A successful submission enables initiation of clinical trials while an unsuccessful submission will stop or slow development, result in additional expenses and cast a dark cloud over the therapeutic candidate.

The path to a successful submission begins early in the development process. It is founded upon a clear understanding of the indication, clinical development path and proposed mechanisms of action of the drug candidate. Upon this intellectual foundation is built a package of data that provides a complete characterization of the candidate including its: chemical properties; safety; toxicity and pharmacokinetics thus allowing for some prediction of its effects in human subjects. In addition to a complete and competently prepared submission package, an understanding and appreciation of Agency’s perspective will minimize the chances for unpleasant surprises.

The purpose of this presentation is to provide a few insights that may help folks avoid being “that case study” that everyone else learns from.
SESSION IV: Strategies for Challenging CNS Targets—Case Study Examples

Hien Tran Zhao, PhD, Ionis Pharmaceuticals, Inc.

Dr. Hien Tran Zhao is an assistant director in neuroscience drug discovery at Ionis Pharmaceuticals, Inc., a company with work in RNA therapeutics. She leads target discovery and validation efforts for neurodegenerative diseases including Alzheimer’s and Parkinson’s disease. Dr. Zhao is passionate about her work and impact on patients.

Dr. Zhao received her PhD in Neuroscience from Washington University in St Louis and her BS in Biochemistry from the University of Houston. Dr. Zhao received her postdoctoral training in Dr. Virginia Lee’s lab, focusing on immunotherapeutic approaches to treat Parkinson’s disease.

Antisense Oligonucleotides for The Treatment of Huntington’s Disease: Lessons Learned from Mice and Non-Human Primates

Hien Tran Zhao

Ionis Pharmaceuticals, Inc., Carlsbad, CA, USA

Huntington’s disease (HD) is a fatal dominantly inherited neurodegenerative disease caused by a CAG expansion in the huntingtin gene, for which there is currently no cure. Antisense oligonucleotides (ASOs) are emerging as a viable therapeutic approach and can be used to selectively target production of many of the toxic proteins involved in currently untreatable neurodegenerative diseases. ASO-mediated suppression of huntingtin mRNA in animal models of HD improves motor phenotype, anxiety, gene expression deficits and survival. One key experiment in translating the rodent work to the clinic is determining the pharmacodynamics and pharmacokinetics of huntingtin-targeting ASOs in a larger brain using IT delivery, the intended clinical route of administration. To this end, we have treated non-human primates (NHP) with an ASO targeting NHP huntingtin at two dose levels and collected tissues 1, 4, or 8 weeks post-dosing. After intrathecal delivery of the huntingtin ASOs, huntingtin mRNA is suppressed throughout the NHP CNS, including cortical regions, thalamus, and caudate, all key regions implicated in HD. Remarkably, target suppression and ASO accumulation are similar in spinal cord adjacent to the injection site and in frontal cortex, the most distal region from the injection site. Target mRNA suppression is sustained and still present 8 weeks post-dosing. Using a novel assay to quantify total huntingtin protein, we also confirmed huntingtin protein levels track with RNA levels. These data support the use of intrathecal dosing to deliver huntingtin-targeting ASOs to the brain regions implicated in HD as a potential therapeutic for the treatment of HD.
SESSION IV: Strategies for Challenging CNS Targets—Case Study Examples

Albert La Spada, MD, PhD, University of California, San Diego School of Medicine

Dr. Albert La Spada is a founding faculty member of the UCSD Institute for Genomic Medicine and Sanford Consortium for Regenerative Medicine and is a Professor and Division Head of Genetics in Pediatrics, Cellular & Molecular Medicine, and Neurosciences at the University of California, San Diego.

While an MD, PhD student at the University of Pennsylvania School of Medicine, Dr. La Spada identified the cause of spinal & bulbar muscular atrophy (SBMA) as an expansion of a trinucleotide repeat in the androgen receptor gene. As the first disorder shown to be caused by an expanded repeat tract, this discovery of a novel type of genetic mutation led to the emergence of new field of study. After completing training as a Clinical Genetics fellow and a Howard Hughes Medical Institute Physician Postdoctoral Fellow, he joined the faculty at the University of Washington Medical Center in 1998, and became a Professor of Laboratory Medicine, Medicine (Medical Genetics), Pathology, and Neurology (Neurogenetics).

Dr. La Spada's research is focused upon neurodegenerative disease, and he is seeking the molecular events that underlie neurodegeneration and neuron cell death in SBMA, Huntington’s Disease, spinocerebellar ataxia type 7, ALS, and Parkinson’s disease. He and his team have uncovered evidence for transcription dysregulation, perturbed bioenergetics, and altered protein quality control as contributing factors in neuron dysfunction. By reproducing molecular pathology in mice and in neurons derived from human patient stem cells, Dr. La Spada has begun to develop therapies to treat these disorders.

Dr. La Spada has been the recipient of grants and awards from the National Institutes of Health, Howard Hughes Medical Institute, Muscular Dystrophy Association, Hereditary Disease Foundation, CHDI, Coulter Foundation, American Federation for Aging Research, Packard Center for ALS Research, and Harrington Discovery Institute. Among his funding awards is the Paul Beeson Physician Faculty Scholar Aging Research Award. In 2006, Dr. La Spada was inducted into the American Society for Clinical Investigation, in 2007, he was bestowed with the Lieberman Award by the Hereditary Disease Foundation for excellence in Huntington’s Disease research, in 2011, he received the Molecular Mechanisms of Neurodegeneration Distinguished Research Award in Milan, Italy, in 2013, he was inducted into the Association of American Physicians, and in 2015, he was selected to be a Gund-Harrington Scholar for his translational research accomplishments.

Repurposing Drugs for Neurodegenerative Diseases

Albert La Spada

University of California, San Diego School of Medicine, San Diego, CA, USA

Neurons constantly demand high levels of energy, and must maintain mitochondrial quality control and proteostasis for optimal function. The PPARs are ligand-activated transcription factors that belong to the nuclear hormone receptor superfamily, and promote mitochondrial biogenesis and oxidative metabolism. We recently determined that transcriptional dysregulation of PPARδ underlies HD, interference with PPARδ function is sufficient to produce neurodegeneration, and PPARδ agonist treatment with the repurposed drug KD3010 is an effective therapy for HD. Another aspect of PPARδ biology with relevance for therapy development is that PPARδ forms a heterodimer with RXR, and RXR agonists are capable of promoting PPARδ transactivation. One compound with potent RXR agonist activity is bexarotene, a FDA-approved cancer drug that was reported to be an effective treatment for Alzheimer’s disease (AD) in a provocative preclinical trial. To determine if bexarotene has therapeutic application in HD, we evaluated the effect of bexarotene on mutant huntingtin protein toxicity, and observed marked neuroprotection — that was dependent upon PPARδ, not PPARγ. We then pursued a preclinical trial of bexarotene in HD mice, and found that bexarotene rescued motor function and neurodegeneration. PPARδ agonist therapy normalized impaired oxidative metabolism in HD neurons, rescued mitochondrial fragmentation, and induced autophagy to prevent huntingtin protein aggregation. Our results indicate that PPARδ agonist therapy using repurposed drugs achieves neuroprotection by promoting both oxidative metabolism and quality control, and thus may represent a therapeutic opportunity for a variety of neurodegenerative disorders, including HD, PD, and AD.
SESSION V: Commercialization Strategies: Developing Science into Products

Chair: Frank Longo, MD, PhD—Stanford University and PharmatrophiX

Intellectual Property for Early Stage Life Science Companies
Laurie McNamara, JD, PhD & Maya Skubatch, JD—Wilson Sonsini Goodrich & Rosati

Lessons Learned in Drug Development from an Academic and Small Biotech Perspective
Frank Longo, MD, PhD—Stanford University & PharmatrophiX

Finding and Working with Industrial Partners
Diana Wetmore, PhD—Harrington Discovery Institute
SESSION V: Commercialization Strategies: Developing Science into Products

Laurie McNamara, JD, PhD, Wilson Sonsini Goodrich & Rosati

Dr. Laurie McNamara is a registered patent attorney, and is an associate in the patents and innovations counseling group at Wilson Sonsini Goodrich & Rosati. She focuses her practice on various aspects of intellectual property law for clients in the pharmaceutical and biotechnology industries. She has provided strategic counseling for clients related to patent prosecution, licensing, diligence, freedom to operate, patentability, invalidity and non-infringement analyses. She has managed global patent dockets and has knowledge of United States and international patent laws.

Dr. McNamara holds a PhD in biochemistry and drug discovery from Northwestern University in which her doctoral research focused on the structural biology of protein kinases involved in neurodegenerative diseases. During graduate school, she gained research experience in protein purification, enzymology, x-ray crystallography, structure-assisted inhibitor design and medicinal chemistry. Before graduate school, she worked at Merck Research Laboratories in Rahway, NJ, in the drug metabolism and basic chemistry departments.

Maya Skubatch, JD, Wilson Sonsini Goodrich & Rosati

Dr. Maya Skubatch is a partner at Wilson Sonsini Goodrich & Rosati, where she focuses on patents and innovations counseling. Her practice covers patent prosecution, strategic patent counseling, investor- and company-side due diligence, and license agreements for clients in the life sciences and clean technology industries.

Prior to joining Wilson Sonsini Goodrich & Rosati, Dr. Skubatch was an associate in the intellectual property litigation practice at Gray Cary Ware & Freidenrich LLP (now DLA Piper) in Palo Alto. While at UC Berkeley, Dr. Skubatch participated in research in the laboratory of Nobel Laureate Professor Randy Scheckman in the Department of Molecular and Cell Biology, where she studied Golgi protein transport in yeast cells. She also participated in research in the laboratory of Professor Sung-Hou Kim in the Department of Chemistry, where she studied various zinc-finger domains. After completing her BA, Dr. Skubatch was a researcher at Genentech, where she helped clone and characterize APO2 ligand, a player in apoptosis signaling.

Intellectual Property for Early Stage Life Science Companies

Laurie McNamara & Maya Skubatch

Wilson Sonsini Goodrich & Rosati, Palo Alto, CA, USA

This presentation will cover best practices for starting a life sciences company and for working with technology transfer offices at universities. This presentation will also cover a brief overview of the patent prosecution process and what to expect when working with IP counsel. The presentation will cover developing an IP strategy, patent filing strategies, maximizing protection of clinical candidates, and IP due diligence.
SESSION V: Commercialization Strategies: Developing Science into Products

Frank Longo, MD, PhD, Stanford University and PharmatrophiX

Dr. Frank Longo is Professor and Chairman, Department of Neurology and Neurological Sciences at Stanford University. He received his MD in 1981 and PhD in Neurosciences in 1983 from UC San Diego. He completed his neurology and fellowship training in the Department of Neurology at UC San Francisco where he was then recruited as an assistant professor and promoted to professor and vice chair. From 2001 to 2005 Dr. Longo 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 (ADDF), Alzheimer’s Association, and the NIH, he and his team have pioneered small molecule treatment strategies for Alzheimer’s and other neurodegenerative diseases. In 2005, while at UNC, he founded PharmatrophiX, a company focused on the commercial development of these therapies. A lead candidate compound for Alzheimer’s disease has completed phase 1 safety trials and is slated for a phase 2a trial in Alzheimer’s patients.

In 2015, Dr. Longo was the recipient of the inaugural Melvin R. Goodes Prize for Excellence in Alzheimer’s Drug Discovery from the ADDF in recognition of his work creating Alzheimer’s disease therapies.

Lessons Learned in Drug Development from an Academic and Small Biotech Perspective
Frank Longo
PharmatrophiX, Menlo Park, CA, USA

Important drug candidates with significant novel clinical potential continue to emerge from translational programs in universities as well as the continuous emergence of small biotech companies. In both settings, there are key important lessons to learn in terms of reaching value inflection points, avoiding common pitfalls and obtaining funding. 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 and execution of intellectual property, target rationale/validation/engagement, quality and translational value of preclinical work, availability of relevant biomarkers, clinical trial plans and/or data); the basics of starting or partnering with a company; following university and conflict-of-interest policies; options for funding; elements of the virtual company model; working with CROs; large pharma partnership models and goals; and exit strategy options.
Dr. Diana Wetmore is Vice President of Therapeutics Development and Director of the Innovation Support Center, and manages the portfolio of scholar projects that are supported by the Harrington Discovery Institute (HDI).

Dr. Wetmore is a business-oriented scientist with a successful history of assembling and guiding complex multi-disciplinary drug discovery collaborations and project teams. At HDI, her portfolio management role is critical for ensuring that the Harrington Innovator, Gund-Harrington, and ADDF-Harrington scholar drug discovery projects have access to support and guidance that will help translate their ideas to the clinic and to patients. A key component of that support is the Innovation Support Center (ISC), which Diana directs. Members of the ISC panel bring pharma expertise and know-how to the portfolio projects with a view to accelerating the development of new therapies.

Dr. Wetmore obtained her PhD in Biochemistry at the University of Calgary, Canada, and did her postdoctoral training at Dupont Merck Pharmaceutical Company. During her more than 20 years in the drug discovery field, she has been part of project teams that yielded multiple INDs and two approved drugs. She has a combination of experience in Pharma, Biotech, and not-for-profit settings acquired in the US and internationally.

Prior to joining Harrington Discovery Institute, Dr. Wetmore served as VP Alliance Management and Operations for Beryllium Discovery, a structure based drug discovery organization, as VP of Business Development and Alliance Management at Cystic Fibrosis Foundation Therapeutics (CFFT) and as Sr. Director of Project Management at Anadys Pharmaceuticals. At CFFT she was an active member of the Vertex project team that led to the two first in class disease modifying therapies Kalydeco™ and Orkambi™. Professional interests include protein structure/function relationships and ligand recognition, strategic planning and building collaborative drug discovery projects.

Finding and Working with Industrial Partners

Diana Wetmore

Harrington Discovery Institute, Cleveland, OH, USA

Now that you have your exciting drug discovery technology identified and your intellectual property protected, what are your next steps to attract the best industry partner and get set up for a successful licensing negotiation?

In this presentation, we will look at three key areas that can make or break an out-licensing campaign: defining and completing your licensable package; marketing the technology to potential partners; and surviving the due diligence process. In addition to an overview of best practices, some practical solutions and specific examples will be used to illustrate concepts.
LEAD SPONSORS

National Institute on Aging – National Institutes of Health’s mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability. The National Institute on Aging (NIA)—one of the 27 Institutes and Centers of the NIH—has been at the forefront of the nation’s research activities dedicated to understanding the nature of aging, supporting the health and well-being of older adults, and extending healthy, active years of life for more people.

Eli Lilly and Company - 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.

Merck & Co. - 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.

PARTNERS

The Harrington Discovery Institute at University Hospitals in Cleveland, Ohio—part of The Harrington Project for Discovery & Development—aims to advance medicine and society by enabling our nation’s most inventive physician-scientists to turn their discoveries into medicines that improve human health. The ADDF-Harrington Scholar Program was established in partnership to leverage the combined expertise and resources of both organizations to advance highly promising Alzheimer’s disease discovery projects conducted in academic medical institutions nationwide. ADDF-Harrington Scholars get funding from ADDF and strategic advising and mentoring from experts in pharmaceutical development through the Harrington Discovery Institute’s Innovation Support Center to chart a path from the bench to the clinic. For more information about Harrington Discovery Institute visit: www.HarringtonDiscovery.org

The National Multiple Sclerosis Society exists because there are people with MS. Our vision is a world free of MS. Everything we do is focused so that people affected by MS can live their best lives as we stop MS in its tracks, restore what has been lost and end MS forever. The Society is a gathering place for people with MS, their family and loved ones, healthcare providers, volunteers, donors, fundraisers, advocates, community leaders and all those that seek a world free of MS.

The Taub Institute for Research on Alzheimer’s Disease and the Aging Brain at Columbia University Medical Center and New York-Presbyterian Hospital brings together researchers and clinicians across disciplines to uncover the causes of Alzheimer’s, Parkinson’s, and other age-related brain diseases, and to discover ways to treat, prevent, and ultimately cure these diseases. In collaboration with the Departments of Pathology & Cell Biology and Neurology, research in the Taub Institute integrates genetic analysis, molecular and cellular studies, and clinical investigation to better understand complex neurodegenerative disorders. Funding for the Taub Institute’s Alzheimer’s Disease Research Center is provided by the NIH/NIA. In 2016, the Taub Institute was designated as a Center of Excellence for Alzheimer’s Disease by the New York State Department of Health. For more information, visit the Taub Institute for Research on Alzheimer’s Disease and the Aging Brain at http://www.cumc.columbia.edu/dept/taub/