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September Meeting

The 898th Meeting of the Northeastern Section of the American Chemical Society

Northeastern Section
American Chemical Society

JOINT MEETING: NORTHEASTERN SECTION, ACS AND MEDICINAL CHEMISTRY GROUP

Symposium
RECENT DEVELOPMENTS IN NEURODEGENERATIVE DISEASES

Organized by the Medicinal Chemistry Section of the Northeastern Section, American Chemical Society

Thursday - September 10th, 2009
Marriott Hotel
One Burlington Mall Road, Burlington, MA.

3.00 pm	Refreshments
3.15 pm	Welcome *Raj (SB) Rajur, Program Chair, CreaGen Biosciences, Inc., Woburn, MA*
3.20 pm	Introductory Remarks *Norton P. Peet, Director of Chemistry, Microbiotix, Worcester, MA*
3.30 pm	**Development of Drugs to Treat Cognitive Disorders** *Alan P. Kaplan, Director of Medicinal Chemistry, Helicon Therapeutics San Diego, CA*
4:15 pm	**Epigenetic Regulation of Memory Formation in Health and Disease** *Li-Huei Tsai, Director, Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA*
5:00 pm	**Optimization of the In Vivo Activity of Potent, Notch-Sparing gamma-Secretase Inhibitors** *Boyd L. Harrison, Sr. Director of Chemical Sciences, Wyeth Research, Princeton, NJ*
5:45 pm	Social Hour
6:30 pm	Dinner
7:45 pm	**Targeting A_42 for Alzheimer's Disease Therapy** *Mark A. Findeis, Co-Founder and Senior Vice President of Research, Satori Pharmaceuticals, Cambridge, MA*

Dinner reservations should be made **no later than 12:00 noon on Thursday, September 3rd, 2009.** Please contact Marilou Cashman at (800) 872-2054 or (508) 653-6329 or mcash0953@aol.com**.** Reservations not canceled at least 24 hours in advance must be paid. Anyone who needs handicapped services/transportation, please call a few days in advance so that suitable arrangements can be made. Reservations not canceled at least 24 hours in advance must be paid. **Payment is made at the door by cash or check (no credit cards.) Members, $28.00; Non-members, $30.00; Retirees, $18.00; Students, $10.00.**

Directions Burlington Marriott

Please use map quest to reach the hotel: Marriott Hotel is located on one Burlington Mall Road, Burlington, MA.

THE PUBLIC IS INVITED

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Alan P. Kaplan
"Development of Drugs to Treat Cognitive Disorders"

In recent years, the search for treatments for cognitive and memory dysfunction has garnered increased interest from drug discovery companies, both big and small. The need for such drugs will only be exacerbated as the baby-boom generation gets older. At this time, the options available to treat memory impairment are inadequate, with a limited number of drugs that, at best, slow the progression of memory decline. HT-0712, a phosphodiesterase IV inhibitor, represents a novel class of drug that shows promise as a potential treatment for cognitive dysfunction due to age, disease or brain injury. In vivo studies with HT-0712 suggest that its use could be efficacious for a number of potential clinical applications, including stroke, traumatic brain injury (TBI), age associated memory impairment (AAMI) and Rubenstein-Taybi Syndrome (RTS).

Alan Kaplan joined Helicon as Director of Chemistry in 2003 and is responsible for both the drug discovery and drug development activities. Prior to joining Helicon, Dr. Kaplan was eight years at ArQule, helping the company establish its high-throughput medicinal chemistry technologies. While at ArQule, Dr. Kaplan worked closely with ArQule's pharmaceutical and biotech partners on a number of drug programs, eventually becoming Senior Director of Lead Optimization Chemistry. Dr. Kaplan pursued postdoctoral training at Harvard University after receiving his Ph.D. in 1991 from the University of California at Berkeley and a B.A. in 1986 from Northwestern University.

Li-Huei Tsai
"Epigenetic regulation of memory formation in health and disease"

Abstract: Neurodegenerative diseases of the central nervous system are often associated with impaired learning and memory, eventually leading to dementia. Currently, effective therapeutic strategies for restoring cognition in these patients are lacking. We have been exploring strategies that facilitate re-establishment of learning ability and access to long-term memories. The CK-p25 transgenic mice previously created in this lab allows temporally and spatially restricted induction of neuronal loss and learning/memory impairment which serves as an ideal model for testing therapeutic strategies. Chromatin modifications, especially histone-tail acetylation, have been implicated in memory formation. Increased histone-tail acetylation induced by inhibitors of histone deacetylases (HDACis) facilitates learning and memory in wildtype mice as well as in mouse models of Rubinstein-Taybi syndrome, a developmental brain disorder. We found that increased histone acetylation as a result of HDACi treatment reinstated learning behavior and re-established access to long-term memories after significant brain atrophy and neuronal loss had already occurred in the CK-p25 mice. Moreover, increased histone acetylation by HDACi induced sprouting of dendrites and increased number of synapses, thus, long-lasting changes of neural circuits which may underlie its beneficial effects on cognition. Currently, all available HDACis target multiple histone deacetylases. Identification of the histone deacetylase family member(s) specifically involved in memory formation will help elucidate the mechanism(s) by which chromatin remodeling regulates memory and allow the development of potent and selective HDACi useful for clinical applications.

Dr. Li-Huei Tsai received her P.h.D degree from the University of Texas Southwestern Medical Center at Dallas. She then took postdoctoral training from Ed Harlow's laboratory at Cold Spring Harbor laboratory and Massachusetts General Hospital. She joined the faculty in the Department of Pathology at Harvard Medical School in 1994 and was named an investigator of Howard Hughes Medical Institute in 1997. In 2006, she was appointed Professor in the Department of Brain and Cognitive Sciences, and joined the Picower Institute for Learning and Memory at MIT. Presently she is serving as the director of this center. She is a recipient of the Rita Allen Foundation Scholarship, a Klingenstein Fellowship for Neurosciences, and a Promising Investigator Award from Metropolitan Life Foundation.

In addition, Li-Huei has authored or co-authored more than 85 publications; she has given a number of invited presentations in universities and at national and international symposia. She also serves as the editorial board of, NeuroSignals, Neuron, the Journal of Neuroscience and the founding editorial board of American Journal of Translational Research. She is *Ad hoc* reviewer for: Cell, Neuron, Nature, Science, Nature Cell Biology, Nature Neuroscience, Nature Genetics, Journal of Neuroscience, Molecular and Cellular Biology, Journal of Neurochemistry, New England Journal of Medicine, Cell Growth and Differentiation, Proceedings of National Academy of Sciences USA, Molecular Biology of Cell

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Boyd L. Harrison,
"Optimization of the In Vivo activity of Potent, Notch-sparing gamma-Secretase Inhibitors"

Abstract: Alzheimer's disease (AD) is among the most devastating human disease for which there is still no highly effective treatment. Currently available AD therapies only provide symptomatic treatment. The proposed causative role for Abeta40 and Abeta42 in the pathophysiology of AD has provided a rational strategy for the design of potential disease-modifying anti-AD drugs (DMAADs). By blocking the synthesis of these putative pathogenic peptides, it is hoped that the progression of AD will be slowed or prevented. We have focused our efforts on inhibition of gamma secretase, the final enzyme in the biosynthesis of Abeta40 and Abeta42 from APP. A caveat with this approach is that selectivity of gamma secretase inhibition of APP processing is required due to the importance of other gamma secretase substrates such as Notch in important physiological processes such as G.I. cell renewal. We have previously reported on the discovery of the Notch-sparing gamma secretase inhibitors (GSIs) that showed limited oral bioavailability in Tg 2576 mice due to rapid in vivo metabolism. By identifying and blocking the sites of metab. of these leads, we have designed and synthesized novel GSIs with potent, oral in vivo activity that also retain Notch-sparing selectivity. The evolution of this series of compounds will be discussed.

Boyd Harrison received a PhD in Organic Chemistry from Rice University in 1971. Following a short tenure at DuPont working in the Jackson Laboratories, he returned to Rice in 1972 where he completed an NSF postdoctoral fellowship/lectureship in the laboratories of the late R. V. Stevens working on the total synthesis of vitamin B-12. In 1974, Boyd joined the R&D division of Merrell-National Labs (now Sanofi-Aventis) in Cincinnati, Ohio as a medicinal chemist. He remained there for 23 years working in the areas of beta-lactam antibiotics, anti-inflammatory compounds, and anti-ischemic (anti-stroke) compounds - three compounds from his laboratory in these research areas advanced to the clinical evaluation stage. During this period, he rose through the ranks to a Senior Group Leader position.

Boyd joined Wyeth Discovery Research in January 1997 as an Associate Director of Medicinal Chemistry in the Chemical Sciences group. He rose to Senior Director of Discovery Medicinal Chemistry in the Chemical Sciences department at Wyeth where he directed the efforts of >25 medicinal chemists, developing novel therapeutics for depression/anxiety, schizophrenia, Alzheimer's Disease, cognition enhancement, and neuropathic pain. In the recent past, his group has provided the initial design, synthesis, and medicinal chemistry support in placing ten (10) compounds onto Development Track. Of these, SCA-136 (schizophrenia), GSI-953 (Alzheimer's Disease), and VRA-175 (neuropathic pain) are currently in active clinical evaluation.

Early in 2009, Boyd became head of the Compound Properties Group, a diverse research group of 21 scientists providing pharmaceutical properties and physical chemical characterization on all requested compounds from the therapeutic areas of Wyeth Discovery. Using a variety of "high throughput" and individual compound property assays, CPG collaborates with project teams and leaders on the selection, and optimization of hits, leads, and advanced compounds with respect to their compound property space. Ultimately, the CPG is committed to assisting Medicinal Chemistry in the optimization of compound Structural Property Relationships (SPR), allowing the advancement of the most efficacious, safest and "drug-like" compounds.

In addition, Boyd is an inventor on >40 granted US patents and US patent applications and has authored or co-authored 56 external publications; he has given a number of invited presentations in universities and at national symposia.

Mark A. Findeis
"Targeting A_42 for Alzheimer's Disease therapy"

Abstract: An expanding body of research has elucidated the central role of amyloid precursor protein (APP) processing and amyloid beta peptide (Abeta) production in the risk, onset, and progression of Alzheimer's disease (AD), the most common form of dementia. Ongoing research is establishing a greater level of detail for our understanding of the normal functions of APP, its proteolysis products, and the mechanisms by which this processing occurs. The importance of this processing machinery in normal cellular function, such as Notch processing, has revealed specific concerns about targeting APP processing for therapeutic purposes. Aspects of AD that are now well studied include direct and indirect genetic and other risk factors for AD, APP processing, and Abeta production. Emerging from these studies is the particular importance of the long form of Abeta, Abeta42. Elevated Abeta42 levels, particularly the elevation of the ratio of Abeta42 to the shorter major form Abeta40, have been identified as important early events in the pathogenesis of AD. The specific pathological importance of Abeta42 has drawn attention to seeking drugs that will selectively lower the levels of this peptide through reduced production or increased clearance while allowing normal protein processing to remain substantially intact.

Mark A. Findeis is Co-Founder and Senior Vice President of Research of Satori Pharmaceuticals Incorporated, a neuroscience company focused on the discovery and development of innovative disease-modifying therapies for Alzheimer's disease and other

neurodegenerative disorders. He has over twenty years of experience in research and development. After his postdoctoral work, he was on the faculty at Harvard Medical School. He then helped to start TargeTech Incorporated, a company using receptor-mediated delivery for gene therapy, antisense therapy and targeted drug delivery. After the acquisition of TargeTech by The Immune Response Corporation, he joined Praecis Pharmaceuticals. As Director of Chemistry at Praecis, he co-directed the discovery program that resulted in the beta-amyloid aggregation antagonist Apan™ for the treatment of Alzheimer's disease. While at Praecis, he also supported the development program of Plenaxis™, an LHRH antagonist that gained FDA approval for the treatment of prostate cancer. Dr. Findeis also managed chemistry for a diverse range of discovery programs at Praecis in the areas of inflammation, cancer, and metabolic diseases. Mark received his academic training at the Massachusetts Institute of Technology, Harvard University and The Rockefeller University.