2003 PROGRAM

8:30 a.m. **Registration and Continental Breakfast Atrium (Room 1-65), William T. Young Library**

9:00 a.m. **Welcome by Dr. Lee T. Todd, Jr., President, University of Kentucky - Auditorium (Room 1-62), William T. Young Library**

9:05 a.m. **Introductory Remarks - Dr. Tae H. Ji, University of Kentucky**

9:10 a.m. **Dr. Susumu Tonegawa, Massachusetts Institute of Technology**
"Memory Recall"

Pattern completion, the ability to retrieve complete memories on the basis of incomplete sets of cues, is a crucial function of biological memory systems. The extensive recurrent connectivity of the CA3 area of hippocampus has led to suggestions that it might provide this function. We have tested this hypothesis by generating and analyzing a genetically engineered mouse strain in which the *N*-methyl-D-asparate (NMDA) receptor gene is ablated specifically in the CA3 pyramidal cells of adult mice. The mutant mice normally acquired and retrieved spatial reference memory in the Morris water maze, but they were impaired in retrieving this memory when presented with a fraction of the original cues. Similarly, hippocampal CA1 pyramidal cells in mutant mice displayed normal place-related activity in a full-cue environment but showed a reduction in activity upon partial cue removal. These results provide direct evidence for CA3 NMDA receptor involvement in associative memory recall.

10:00 a.m. **Poster Session, Room 137, Chemistry-Physics Building**

11:45 a.m. **Buffet Lunch, Faculty Club [Please return registration card by April 11, 2003 for reservations]**

1:00 p.m. **Dr. Richard Mains, University of Connecticut Health Center**
"Kalirin and Trio: A Medley of Interactors"

Precise control of the actin cytoskeleton is critical to many cellular functions; members of the Rho subfamily of small GTP binding proteins play essential roles in this process. In addition to GTPase activating factors (GAPs), GDP/GTP exchange factors (GEFs) of the Dbl family are critical to the activation of the large family of Rho proteins. While most Rho GEFs have a single Dbl homology (DH) domain, Kalirin and Trio define a small family of structurally related dual GEF proteins, facilitating the coordinate regulation of multiple Rho family members. In addition to their two DH domains, both have a Sec14p domain, 9 spectrin-like repeats, 2 pleckstrin homology domains, 2 SH3 domains, an Ig-fibronectin region and a putative kinase domain. The gene encoding Kalirin uses multiple promoters and alternative splicing to generate over a dozen different combinations of functional domains. The spectrin-like region of Kalirin and Trio is the site of interaction with peptidylglycine alpha-amidating monooxygenase (a secretory granule enzyme), the inducible form of nitric acid synthase, and huntingtin associated protein. The first GEF domain of Kalirin and Trio activates Rac1 and RhoG while the second GEF domain activates RhoA. Expression of dual GEF isoforms of Kalirin causes exuberant outgrowth of axons from sympathetic neurons while expression of a mono GEF isoform of Kalirin greatly increases the number of dendritic spines in hippocampal and cortical neurons. Importantly, antisense-mediated reductions in Kalirin expression result in spine retraction and in collapse of the dendritic arbor. Kalirin and Trio may play pivotal roles in signaling between a wide variety of extracellular signals and the actin cytoskeleton.

1:50 p.m. **Break**

2:00 p.m. **Dr. Ashley I. Bush, Massachusetts General Hospital and Harvard Medical School**
"Metal Ions, β-Amyloids and Alzheimer's Disease"

Aβ is the principal component of the plaque pathology which is the hallmark of Alzheimer's disease (AD). We have characterized Aβ as a ubiquitous metalloprotein, with selective high-affinity binding sites for zinc (Ka≈ 100 nM) and copper (Ka≈ 10 attoM). Several studies have reported that there is an elevation of zinc and copper in the plaques in Alzheimer's disease. Furthermore, genetic ablation of the ZnT3 transporter, which loads zinc into the glutamatergic synapse, abolishes amyloid deposition in the Tg2576 mouse model for AD.

Aβ binds Cu and Zn through a site that involves oligomeric peptide assembly, and resembles the structure of SOD1. When synthetic Aβ binds copper in the absence of zinc, it is highly redox active. Biological reducing agents such as dopamine, cholesterol and vitamin C can act as a reservoir of electron donation, so that the Aβ/Cu complex acts as a catalyst generating H_2O_2 (Km= 5 μM, Vmax= 30 nM/min). The toxicity of Aβ species is proportional to the peptide's ability to reduce Cu or Fe and generate H_2O_2 (Aβ42> Aβ40 >rat Aβ).

Chelators of copper and zinc both disaggreagate Aβ deposits from post-mortem human brain and also inhibit H_2O_2 production. We have recently found that one such orally bioavailable chelator, clioquinol, markedly inhibits brain amyloid pathology in Tg2576 mice. This compound is a retired antibiotic and has recently completed a Phase 2 clinical trial in Alzheimer's disease.

3:00 p.m. **Reception and Meet with Speakers, Atrium (Room 1-65), William T. Young Library**

(http://www.chem.uky.edu/seminars/naff/welcome.html)

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Twenty-Ninth Annual
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Anna S. Naff

Neuroscience

SPEAKERS

Susumu Tonegawa
Richard E. Mains
Ashley I. Bush

Friday, April 18, 2003

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