PHILADELPHIA ORGANIC CHEMISTS' CLUB

DATE: Thursday, February 24th, 2005; 6:00 pm dinner, 8:00 pm seminar

PLACE: Room 102, New Chemistry Building, University of Pennsylvania, 34th and Spruce Streets, Philadelphia, PA

SPEAKER: **Dr.** Robert L. Hudkins, Associate Director of Medicinal Chemistry, Cephalon

BIOGRAPHY: Robert L. Hudkins is from Virginia Beach, Virginia. He obtained his Ph.D. in Medicinal Chemistry from the Medical College of Virginia/Virginia Commonwealth, University, his M.S. in Organic Chemistry from Old Dominion University, Norfolk, VA, and his B.S. in Chemistry from Atlantic Christian College, Wilson, NC. He has been employed in the pharmaceutical industry for over 16 years, with the last 12 years at Cephalon where he is currently an Associate Director of Medicinal Chemistry. His research interests include the design and synthesis of CNS active agents and structure-based design of selective kinase inhibitors for oncology and neurology, where he has been the primary inventor of two compounds and advanced three kinase inhibitors into clinical trials. He has 25 issued U.S. patents, over 100 publications, abstracts and presentations, and serves on the editorial advisory board for five journals.

TITLE: **The Discovery of CEP-1347, a Mixed Lineage Kinase Inhibitor for the Treatment of Parkinson's Disease.**

DINNER: The meeting will be preceded by cocktails (cash bar) at 5:30 pm followed by a dinner at 6:00 pm at Penne Restaurant & Bar, 3601 Walnut Street. Reservations should be made by email: emichelotti@locuspharma.com or phone: (215)-358-2026 to Enrique Michelotti **before 5:00 pm, Monday, January 21st. Please pay the $45.00 for dinner when you attend. Thank you.**

Dr. Robert L. Hudkins, Associate Director of Medicinal Chemistry, Cephalon

ABSTRACT

The only current treatment for Parkinson's (PD) and Alzheimer's disease (AD) involves neurotransmitter replacement therapy, an approach that has shown marginal benefit, and is often beset with initial success followed by disappointing drug ineffectiveness. A major unmet medical need for PD and AD, and the ultimate objective for neurodegenerative disease therapy, is to obtain functional recovery while halting or slowing the disease progression and neuronal loss. Parkinson's disease is a progressive disorder involving the specific degeneration and death of dopamine neurons in the nigrostriatal pathway. Clinical evidence shows that the dopaminergic neurons in the substantia nigra undergo cell death by apoptotic processes. The c-Jun NH_2-terminal kinase (JNK) pathway, leading to activation of the transcription factor c-Jun, has been implicated in neuronal apoptosis, and may contribute to the neuronal cell loss observed in a variety of neurodegenerative diseases including Parkinson's disease. The JNKs are stress activated protein kinases (SAPK) that belong to the mitogen activated protein kinase (MAPK) superfamily. The JNKs are the only kinases known to activate c-Jun and their activity is regulated through a sequential signaling cascade by a series of upstream kinases including the mixed lineage kinases (MLKs). Our research over the last 10 years has focused on developing inhibitors of the MLK family and understanding the role of the MLKs in disease.

CEP-1347, a semi-synthetic derivative of the indolocarbazole natural product (+)K-252a, is currently in late phase III clinical trials for Parkinson's disease. CEP-1347 is an inhibitor of the JNK signaling cascade via MLK inhibition and displays a broad neuroprotective profile. Presented will be the chemistry and preclinical biology data that supported the advancement of CEP-1347 into human clinical trials.

Key references:

Saporito, M. A.; Hudkins, R. L.; Maroney, A. C. Discovery of CEP-1347: An inhibitor of the cJun N-terminal kinase pathway for the treatment of neurodegenerative diseases. *Progress in Medicinal Chemistry*, **2002**, *40*, 23-62.

Maroney, A. C.; Saporito, M. A.; Hudkins, R. L. Mixed Lineage Kinase Family, potential targets for preventing neurodegeneration. *Current Medicinal Chemistry – CNS Agents*, **2002**, *2*, 143-155.

Bozycko-Coyne D.; Saporito, M. S.; Hudkins, R. L. Targeting the JNK pathway for therapeutic benefit in CNS disease. *Current Drug Targets - CNS and Neurological Disorders*, **2002**, *1*, 31-49.

Murakata, C.; Kaneko, M.; Hudkins, R. L. *et al.* Mixed Lineage kinase activity of indolocarbazole analogs. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 147-150.

Kaneko, M.; Hudkins, R. L., *et al.* Neurotrophic 3,9-bis[(alkylthiomethyl]- and -[bis(alkoxymethyl)]-K-252a Derivatives. *J. Med. Chem.* **1997**, *40*, 1863-1869.