Houk-Jung
Organic Colloquium

"Novel GABA- and Ornithine Aminotransferase Inactivators and Potential New Treatments for Epilepsy, Addiction, Neuropathic Pain, and Hepatocellular Carcinoma"

Abstract: An imbalance in the levels of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) and the excitatory neurotransmitter L-glutamate can lead to convulsions. Inhibition of γ-aminobutyric acid aminotransferase (GABA-AT), the enzyme responsible for the degradation of GABA, increases brain GABA levels, which has been shown to produce an anticonvulsant effect. Reduced brain GABA concentration also is a feature of neuropathic pain. A sharp rise in dopamine release is associated with a variety of addictive behaviors. This dopamine release can be attenuated by an increase in GABA; therefore, inactivation of GABA-AT also has an effect on addictive behavior. Inactivation of a related enzyme, ornithine aminotransferase (OAT) in hepatocellular carcinoma (HCC) has been shown to slow the growth of this cancer. In this lecture the design and mechanism of some of our GABA-AT inactivators will be discussed and how these compounds led to the design and discovery of CPP-115 and OV329, potent inactivators of GABA-AT, which have been found to have excellent pharmacokinetic and pharmacological properties for the potential treatment of epilepsy, neuropathic pain, and addiction. An analog related to CPP-115 was identified that does not inactivate GABA-AT but is a potent inactivator of OAT. Enzyme inactivator design and mechanism studies will be discussed, as well as in vitro and in vivo efficacy and pharmacokinetic results, toxicology studies, and a clinical trial with CPP-115.

Prof. Richard B. Silverman
Department of Chemistry
Northwestern University

UCLA College | Physical Sciences
Chemistry & Biochemistry

Thursday, January 21, 2021
4:00 PM | ZOOM

Questions: jgonzalez@chem.ucla.edu