University of Minnesota
Driven to Discover℠

Department of Chemistry

Seminar

9:45 a.m. Tuesday, April 28 • 331 Smith Hall

Professor

Kevan Shokat

Professor and Chair
Department of Cellular & Molecular Pharmacology
University of California, San Francisco

Non-Traditional Strategies for Drugging Traditional Targets: Kinases and GTPases

Research focused on the discovery of new chemical based tools to decipher cellular signaling networks with an emphasis on protein kinases and more recently, GTPases.
Website: http://shokatlab.ucsf.edu/index.htm

Abstract

Somatic mutations in the small GTPase K-Ras are the most common activating lesions found in human cancer, and are generally associated with poor response tostandard therapies. Efforts to directly target this oncogene have faced difficulties due to its picomolar affinity for GTP/GDP and the absence of known allosteric regulatory sites. Oncogenic mutations result in functional activation of Ras family proteins by impairing GTP hydrolysis. With diminished regulation by GTPase activity, the nucleotide state of Ras becomes more dependent upon relative nucleotide affinity and concentration. This gives GTP an advantage over GDP and increases the proportion of active GTP-bound Ras. I will discuss the development of small molecules that irreversibly bind to a common oncogenic mutant, K-RasG12C. These compounds rely on the mutant cysteine for binding and therefore donot affect the wild type protein (WT). Crystallographic studies reveal the formation of a new pocket that is not apparent in previous structures of Ras, beneath the effector binding switch-II region. These data provide structure based validation of a novel allosteric regulatory site on Ras that is targetable in a mutant-specific manner.

Host: Professor William Pomerantz
Refreshments will be served prior to the seminar.