CSCB
Cancer and Stem Cell Biology

CSCB Seminar Series

Title:

"Lessons learned from TKI resistance in chronic myeloid leukemia."

Abstract:

Resistance to tyrosine kinase inhibitors (TKIs) in CML is categorized as BCR-ABL1-dependent or BCR-ABL1-independent. In the case of BCR-ABL1 dependence, there is reactivation of kinase activity, typically as a result of acquired point mutations in the kinase domain of BCR-ABL1. The spectrum of escape mutations is dependent on the type of TKI, which implies that the BCR-ABL1 genotype can be used to rationalize salvage TKI selection. In aggregate first generation (imatinib) and second generation TKIs (nilotinib, dasatinib, bosutinib) cover all single mutants except the T315I mutant of the gatekeeper position. Ponatinib, the only third-line inhibitor currently approved, has activity against all single mutants including T315I, but is vulnerable to T315I-inclusive compound mutations that occur on the same BCR-ABL1 allele. In the case BCR-ABL1-independent resistance, alternative pathways are activated that maintain survival and proliferation despite continued inhibition of BCR-ABL1 kinase activity. Diverse escape pathways have been implicated, posing a significant obstacle to the development of effective and rationale strategies to overcome this type of resistance. Improvement may be possible through identification of critical signaling nodes such as pSTAT3 that are targeted by diverse upstream pathways. Interestingly, resistance in other malignancies with activated tyrosine kinase signaling as oncogenic drivers follows similar patterns, implicating CML as a useful paradigm to understand and overcome TKI resistance in cancer in general.

Date:

20 Jan 2015 (Tuesday)

Time:

1:00 PM to 2:00 PM

(Refreshment will be served by 12:30 PM)

Venue:

Academia @ SGH

Seminar Room L1-S4,
20 College Road, S169856

Host:

Charles Chuah
Assistant Professor
Program in Cancer & Stem Cell Biology
Duke-NUS Graduate medical School Singapore

"No registration is required."
Any enquiry, please contact:
Jamie Liew (Tel: 6516 6954)

DUKE NUS
GRADUATE MEDICAL SCHOOL SINGAPORE

Speaker:

Michael W. Deininger
Professor and Chief
Hematology and Hematologic Malignancies
Department of Internal Medicine
Huntsman Cancer Institute (HCI)
University of Utah

Biography:

Dr. Deininger received his MD from the University of Würzburg Medical School, Germany and his PhD from Imperial College, London. He trained in hematology/oncology. In 2002 he was recruited to Oregon Health & Science University (OHSU). In 2010 Dr. Deininger became the M.M. Wintrobe Professor of Medicine at the University of Utah and was appointed Chief of the Division of Hematology and Hematologic Malignancies and subsequently Senior Director for Transdisciplinary Research at the Huntsman Cancer Institute.

As a clinician-scientist Dr. Deininger is heading an extramurally funded laboratory that is dedicated to the study of signaling pathways, drug resistance and new molecular therapies in leukemia. Dr. Deininger's work describing the selective effects of imatinib on CML cells helped to provide the rationale for clinical trials that led to its regulatory approval. Current work in his lab is focused on understanding the role of the bone marrow microenvironment in leukemia drug resistance and discovering novel therapeutic targets. Dr. Deininger's work encompasses more than 200 articles in the peer-reviewed literature, including leading journals like Cancer Cell and the New England Journal of Medicine. He has contributed book chapters to eminent textbooks such as deVita's Principles of Oncology, is a regular speaker at major international scientific conferences and is a peer reviewer for journals like Nature, Nature Genetics and Cancer Cell.