

CANCER SCIENCE INSTITUTE OF SINGAPORE

DISTINGUISHED SPEAKERS' SERIES 2015

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Cyclin C is a Haploinsufficient Tumor Suppressor

Date: Tuesday, 31 March 2015

Time: 11.30am – 12.30pm

Venue: LT35, Level 1 Auditorium, Centre for Translational Medicine
 (14 Medical Drive, Singapore 117599)

Chair: Dr. Takaomi Sanda

Abstract:

Cyclin C was cloned as a growth-promoting G1 cyclin, and was also shown to regulate gene transcription. We found that in vivo cyclin C acts as a haploinsufficient tumor suppressor, by controlling Notch1 oncogene levels. Cyclin C activates an “orphan” CDK19 kinase, as well as CDK8 and CDK3. These cyclin C-CDK complexes phosphorylate Notch1 intracellular domain (ICN1) and promote ICN1 degradation. Genetic ablation of cyclin C blocks ICN1 phosphorylation in vivo, thereby elevating ICN1 levels in cyclin C-knockout mice. Cyclin C ablation or heterozygosity collaborate with other oncogenic lesions and accelerate development of T cell-acute lymphoblastic leukemia (T-ALL). Furthermore, the cyclin C gene is heterozygously deleted in a significant fraction of human T-ALL, and these tumors express reduced cyclin C levels. We also described point mutations in human T-ALL that render cyclin C-CDK unable to phosphorylate ICN1. Hence, tumor cells may develop different strategies to evade cyclin C inhibitory function.

Biography:

Dr. Peter Sicinski was born in Warsaw, Poland where he got his M.D. and Ph.D. degrees from the Warsaw Medical School. He was a visiting scientist at MRC Molecular Neurobiology Unit in Cambridge, England for two years. Subsequently, he did his postdoctoral training with Dr. Robert A. Weinberg at the Whitehead Institute in Cambridge, Mass. In 1997 Dr. Sicinski joined the Dana-Farber Cancer Institute and Harvard Medical School as an Assistant Professor, and was then promoted to Associate and Full Professor. Dr. Sicinski is currently a Professor of Genetics at Harvard Medical School. His laboratory is investigating cell cycle machinery in development and in cancer.