Biomedical Sciences Institutes
A*STAR

p53 Laboratory Seminar Announcement

- All Are Welcome -

Speaker: **Dr Lyubomir T. Vassilev**
Distinguished Research Leader, Oncology Division of Roche, Nutley, New Jersey

Title : ***"MDM2 and MDMX inhibitors for cancer therapy "***

Date : **20 February 2012 (Monday)**

Time : **11.00am – 12.00pm**

Venue : **Breakthrough Theatrette, Matrix Level 4, Biopolis**

Host : **Prof Sir David Lane**
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Abstract:
The p53 tumor suppressor is controlled by MDM2 and MDMX which bind p53 and negatively modulates its transcriptional activity and stability. Many tumors overproduce MDM2 or MDMX to impair p53 function. Small-molecule MDM2 antagonists, the nutlins, interact specifically with the p53-binding pocket of MDM2 and can release p53 from negative control thus stabilizing p53 and activating the p53 pathway. However, nutlins do not inhibit the p53-MDMX interaction and their effectiveness can be compromised in tumors overexpressing MDMX. Nutlin disrupt p53-MDM2 autoregulatory circuit leading to upregulation of both proteins. They selectively block MDM2-p53 binding but do not affect E3 ligase activity of MDM2. As a result, nutlin treatment facilitates the degradation of MDMX in many cancer cell lines. However, tumor cells that overexpress MDMX are resistant to nutlin. We identified small molecules that potently block p53 interaction with both MDM2 and MDMX by inhibitor-driven homo- and/or hetero-dimerization of MDM2 and MDMX proteins. Structural studies revealed that the inhibitors bind into and occlude p53 pockets of MDM2 and/or MDMX by inducing the formation of dimeric protein complexes kept together by a dimeric small-molecule core. This mode of action effectively stabilized p53 and activated p53 signaling in cancer cells, leading to cell cycle arrest and apoptosis. The dual MDM2/MDMX antagonist, RO-5963, restored p53 apoptotic activity in the presence of high levels of MDMX and may offer a more effective therapeutic modality for MDMX overexpressing cancers.

About the Speaker:
Dr. Lyubomir Vassilev is a Distinguished Research Leader in the Oncology Division of Roche, Nutley, New Jersey. He has 18 years of experience in leading small-molecule drug discovery efforts in Oncology. Dr. Vassilev's expertise covers the whole spectrum of activities involved in the discovery and development of cancer therapeutics: discovery and validation of molecular targets, assay development and high throughput screening, identification and optimization of drug leads. His primary research interests include mechanisms of signal transduction and cell cycle control and their deregulation in cancer. Dr. Vassilev received his Ph.D. degree in Molecular Biology from the Institute of Molecular Biology, Bulgarian Academy of Sciences where he worked on the structure and function of chromatin. He did his post-doctoral training at the Brookdale Center for Molecular Biology, Mount Sinai School of Medicine, New York, NY and the Roche Institute of Molecular Biology, Nutley, NJ working on the mechanisms of mammalian DNA replication. He has authored or co-authored 70 research and review articles.