IMCB Invited Speaker

Speaker : **Dr. Ramanuj DasGupta**

Scientific Director, RNAi Facility & Assistant Professor,
Departments of Biochemistry and Molecular Pharmacology,
New York University School of Medicine, USA

Date : 10 October 2012 (Wednesday)

Time : 11:00AM - 12:00PM

Venue : Level 3, IMCB Seminar Room 3-46, Proteos, Biopolis

Host : Dr. Frederic Bard

Seminar :

RNAi-based modifier screens to identify novel small molecule and microRNA modulators of the Wnt/wingless signaling pathway

The Wnt/wingless (wg) pathway is one of a core set of evolutionarily conserved signaling pathways that regulate many aspects of metazoan development. Inappropriate activation of the Wnt pathway has been associated with tumorigenesis of the liver, colon, breast and skin. One of the most important effectors of the Wnt pathway is encoded by the transcription factor, beta-catenin (ß-cat)/armadillo (arm). Since β-catenin Responsive Transcription (CRT) has been implicated in the genesis of many cancers, it makes an ideal target for developing therapeutics that could be utilized to modulate the nuclear activity of ß-cat. We employed a novel cell-based chemical genetic high-throughput screening (HTS) methodology, where we screened for small molecule "modifiers" of RNAi-induced loss-of-function phenotypes of genes that are commonly mutated in cancers associated with enhanced Wnt/β-cat activity. In a screen of 15,000 compounds, we identified 3 potent inhibitors of CRT, called iCRT3, iCRT5 and iCRT14. We demonstrate that iCRTs specifically and potently inhibit Wnt/β-cat-induced phenotypes in a variety of Wnt-responsive cell lines, including C57mg mouse mammary epithelial cells and MCF7 human breast adenocarcinoma cell lines. Mechanistic studies suggest that the iCRTs directly bind to β-cat and disrupt its interaction with its transcriptional partner TCF4. Importantly, the iCRTs inhibit cell growth/proliferation of pathologically relevant and oncogene/β-cat-addicted colon cancer cells (such HCT116, HT29, SW480), both in vitro and in xenograft models in vivo. Notably, iCRT3 displayed potent cytotoxic effect on patient-derived primary tumor cells from a variety of cancers at concentrations that are comparable to known FDA-approved chemotherapeutics that are currently in use for treatment. These studies have now enabled us to investigate the putative function of dysregulated Wnt signaling in a variety of cancers whether the role for oncogenic β-cat activity has remained underexplored. Finally, we have used a similar screening approach to identify novel microRNA modulators of the Wnt pathway, which together with expression profiling studies that are currently underway, should enable us to develop novel miRNA-based therapeutics and/or companion-diagnostics that may be used to better predict tumor progression in patients.

About the Speaker :

Dr. DasGupta received his education in New Delhi where he started off as a synthetic organic chemist [(B. Sc. Hons.) from St. Stephen's College, Delhi University (1991-94)]. He switched to Developmental Genetics when he went to Cambridge University, UK, as a Cambridge Commonwealth Trust/Nehru Scholar, where he obtained a B. A. in Genetics (1994-96). He went to University of Chicago where he worked under the guidance of Dr. Elaine Fuchs to obtain his Ph. D. (1996-2002). As a postdoctoral fellow in Dr. Norbert Perrimon's lab at the Harvard Medical School (2002-2005), he was part of the team that established some of the first RNAi-based high-throughput screens (HTS) for cell signaling pathways, using Drosophila cell-based assays. Dr. DasGupta established his independent research program at the NYU School of Medicine/Cancer Institute in early 2006, where he has been ever since. He also established the NYU-RNAi screening center (as its Scientific Director), which offers whole genome cross-species siRNA/shRNA-based libraries for researchers interested in employing HTS/HCS technologies to investigate their favorite biological questions.

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