Institute of Molecular and Cell Biology
A*STAR

SEMINAR ANNOUNCEMENT

We would like to invite you to attend this seminar hosted by Dr. Marius Sudol:

Date: 27 September 2018, Thursday
Time: 2:00PM – 3:00PM
Venue: Level 4, Exploration Theatrette, Matrix, Biopolis

Speaker: Prof. Hisataka Sabe, Department of Molecular Biology, Hokkaido University Graduate School of Medicine, Sapporo, Japan
Title: Pancreatic *KRAS* and *TP53* oncogenes cooperatively activate Arf6-AMAP1 pathway to drive malignancy and immune evasion

Pancreatic ductal carcinomas (PDACs) have been extensively studied regarding their genomic alterations, tumor-microenvironmental intercommunication, and metabolic reprogramming. However, identification of the protein machinery of PDACs that eventually drive malignancy as a result of driver oncogenes and associated events are highly anticipated toward the development of precision medicine. The lack of such information might have hindered elucidation of mechanisms driving malignancies, leaving them incurable. We have shown previously that Arf6 and its effector AMAP1 promote invasion and metastasis of different types of cancers, if overexpressed and hyperactivated. Receptor tyrosine kinases activate Arf6, in which the mevalonate pathway (MVP) is essential. We recently identified that *KRAS* and *TP53* oncogenes, the major driver mutations of PDAC, generate and help activating the Arf6 pathway in PDACs. Our results identify that cooperation between eIF4A/4E-dependent mRNA translation and MVP is a link by which pancreatic driver oncogenes promote invasion and metastasis, via empowering the Arf6-AMAP1 pathway. This pathway was moreover found to be critical to the immune evasion. High expression of the Arf6 pathway components in primary PDACs correlated with poor outcome of the patients. Therefore, our results indicated that malignancies of many PDACs may advance even during early phases of oncogenesis via the Arf6 pathway; and provide therapeutic opportunities towards precise treatments.

Biography:
Professor Sabe has been the head of the Department of Molecular Biology since 2009, and worked to elucidate the molecular mechanisms driving the malignant evolution of metastatic breast cancer, renal cancer, and pancreatic cancer. Dr. Sabe's research achievements include 1) the discovery of the ARF6-based signaling pathway, frequently overexpressed in cancers to drive invasion and metastasis, and 2) the elucidation that the Arf6-based pathway is also essential in promoting cancer malignancy, as well as drug-resistance via its involvement in mitochondrial dynamics and metabolic remodeling. Of particular interest is that Dr. Sabe found that lysophosphatidic acid is the major factor promoting renal cancer malignancy, in which the major factors that externally drive malignancy had remained unknown. He also discovered that the

mevalonate pathway is essential to activate Arf6 and hence essential to cancer malignancy development. These findings have invariably attracted media attention because they raise expectations for clinical applications.