# The role of Cancer Stem Cells in HCC Progression and Treatment-resistance

**Taro Yamashita**

**Clinical Associate Professor, Department of General Medicine, Kanazawa University Hospital**

Carcinogenesis could be characterized as deregulated malignant organogenesis mediated by abnormally proliferating and/or metastatic cancer cells and activated stromal cells that trigger angiogenesis, fibrosis, and inflammation at site. Liver cancer development may recapitulate fetal liver development in part in terms of emergence of cells expressing certain stem cell markers and the activation of signaling pathways during the liver development. We have demonstrated that expression status of hepatic stem/progenitor cell markers may correlate with the clinical outcome in hepatocellular carcinoma patients in terms of vascular invasion and distant organ metastasis using microarray and immunohistochemistry data. Furthermore, we have recently revealed that gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging is a powerful tool to evaluate the maturational status of hepatocellular carcinoma with good prognosis with activation of transcriptional program mediated by hepatocyte nuclear factor 4 alpha. Importantly, stem/maturational status of hepatocellular carcinoma was closely associated with the activation of certain signaling pathways and transcriptional programs such as FOXM1, Wnt, SALL4, and histone deacetylase. Some of these pathways may be targeted by small molecules, and we have identified the different chemosensitivities against a histone deacetylase inhibitor, a poly (ADP-ribose) polymerase inhibitor, imatinib mesylate, and sorafenib tosylate in EpCAM+ and CD90+ hepatocellular carcinoma cells. Our studies demonstrated the importance of evaluating stem/maturational status in hepatocellular carcinoma, paving the way toward new treatment strategies for advanced hepatocellular carcinoma patients with poor prognosis.