ID No.	K2007
Project Title	Analysis of plethora of ASXL functions under physiological and pathological conditions
Principal Investigator	Omar Abdel-Wahab (Associate Member, Memorial Sloan Kettering Cancer Center)
Project Members IMSUT Host Researcher	Toshio Kitamura (Prof., IMSUT)
Members	Susumu Goyama (Prof., Univ. of Tokyo) Daichi Inoue (Group Leader, Foundation of Biomedical Research and Innovation at Kobe (FBRI)) Susumu Kobayashi (Graduate Student, FBRI) Atsushi Tanaka (Graduate Student, FBRI) Muran Xiao (Graduate Student, FBRI)

Report

1. We found that a transcription factor HHEX, one of the common integration sites in the insertional mutagenesis, is able to collaborate with ASXL1-MT (ASXL1 mutant) in inducing leukemia (Takeda et al. Blood 2020).
2. We cloned cDNAs for Xenopus ASXL1, ASXL3 and BAP1. Interestingly, Xenopus ASXL1 lacks the C terminal part which is supposed to be deleted in ASXL1-MT protein while ASXL3 retains that part. We generated polyclonal antibodies against Xenopus ASXL1 and BAP1. Unfortunately, however, the antibody could not detect ASXL1 and BAP1 in Xenopus oocyte extracts.
3. We investigated the ASXL1-MT-KI mouse as a model for clonal hematopoiesis, and found that ASXL1-MT activated Akt by directly binding and stabilizing phosphorylated Akt and induced DNA damage by enhancing cell cycle progression. Mitochondria is also activated and ROS is increased. When ROS was neutralized by N-acetyl cysteine, DNA damage was attenuated. Thus, ASXL1-MT induces DNA damages via pAKT activation, cell cycle progression, activation of mitochondria and increased ROS.