27O-ISMS34 **Identification of Bis-heteroaryl Pyrazoles as Potent ALK2 (R206H) Inhibitors for Treatment of Fibrodysplasia Ossificanas Progressiva (FOP)**

○Katsuhiko SEKIMATA[1], Tomohiro SATO[2], Naoki SAKAI[3], Hisami WATANABE[3], Chiemi MISHIMA-TSUMAGARI[3], Tomonori TAGURI[1], Takehisa MATSUMOTO[3], Noriko HANDA[4], Teruki HONMA[2], Akiko TANAKA[3], Mikako SHIROUZU[3], Shigeyuki YOKOYAMA[4], Yoshinobu HASHIZUME[5], Kohei MIYAZONO[6], Hiroo KOYAMA[1]

[1]Drug Discovery Chemistry Platform Unit, RIKEN Center for Life Science Technologies, [2]Drug Discovery Computational Chemistry Platform Unit, RIKEN Center for Life Science Technologies, [3]Drug Discovery Structural Biology Platform Unit, RIKEN Center for Life Science Technologies, [4]Crystallographic Drug Discovery Platform Unit, RIKEN Systems and Structural Biology Center, [5]RIKEN Program for Drug Discovery and Medical Technology Platforms, [6]Department of Molecular Pathology, Graduate School, The University of Tokyo

FOP is a rare disease of progressive heterotopic ossification in muscles, tendons, or ligaments with an incidence of 1 in 2 million individuals. FOP is caused by abnormal activation of a bone morphogenic proteins (BMP) signaling due to highly recurrent mutations including R206H in a intercellular glycine-serine-rich domain and kinase domain of Activin receptor-like kinase-2 (ALK2), a subtype of BMP type-I receptors. Thus, inhibition of BMP signaling, which is targeting ALK2 (R206H), might lead to a treatment or prevention for FOP.

A novel series of bis-heteroaryl pyrazole has been developed as potent ALK2 (R206H) inhibitors starting from *In silico* screening hit compounds using docking simulation studies, X-ray crystallographic analysis, and medicinal chemistry techniques.