GS02-4 **Identification of a selective HDAC3 inhibitor and a new pharmacophore for KDM inhibitors**

○ Pattaporn JAIKHAN[1], Yukihiro ITOH[1], Takayoshi SUZUKI[1]
[1]Kyoto Prefectural University of Medicine

The post-translational histone modifications such as acetylation/methylation play a vital role in the epigenetic gene expression, and abnormalities of the modifications are involved in various diseases. Accordingly, compounds that can modulate the modifications have attracted much attention as therapeutic agents. On these backgrounds, we have identified some inhibitors against histone modification enzymes. In this symposium, we present our drug discovery studies on Zn^{2+}-dependent deacetylase (HDAC) and Fe^{2+}-dependent lysine demethylase (KDM).

HDAC3, one of the Zn^{2+}-dependent HDACs, is associated with neurodegenerative disorders, and its inhibitors are of interest as therapeutic agents for those diseases. To identify HDAC3-selective inhibitors, a click chemistry-based Zn^{2+}-chelator library was constructed and screened in HDAC assays. As a result, we identified **T247**, bearing an *o*-amino anilide scaffold, as an HDAC3-selective inhibitor and found that it showed the memory enhancement effect *in vivo*. Next, we also challenged identification of inhibitors against KDM5, which is one of Fe^{2+}-dependent KDMs and is associated with cancer drug-resistance. Based on the Zn^{2+}-chelating group of **T247**, a library of *o*-substituted anilides which are expected as Fe^{2+}-chelators was designed and screened in KDM5A assay. An *o*-hydroxy anilide, **1c** inhibited KDM5A and could increase a level of H3K4me3, which is a substrate of KDM5A, in cellular assay. Thus, we suggested that HDAC3-selective inhibitors are expected as therapeutic agents for neurodegenerative disorders and that the *o*-hydroxy anilide is useful for a pharmacophore of KDM inhibitors.