27O-ISMS17 **Synthetic Posttranslational Modifications: A Chemical Catalyst System to Directly Introduce Posttranslational Modifications into Endogenous Chromatin**

○Kenzo YAMATSUGU[1,2], Yoshifumi AMAMOTO[1,2], Yuki AOI[1,2], Nozomu NAGASHIMA[1], Hiroki SUTO[1,2], Daisuke YOSHIDOME[3], Yasuhiro ARIMURA[4], Akihisa OSAKABE[4], Daiki KATO[4], Hitoshi KURUMIZAKA[4], Shigehiro A. KAWASHIMA[1,2], Motomu KANAI[1]

[1]Graduate School of Pharmaceutical Sciences, The University of Tokyo, [2]JST-ERATO, [3]Schrödinger K. K., [4]Laboratory of Structural Biology, Graduate School of Advanced Science and Engineering, Waseda University

Posttranslational modifications (PTMs) of histones play an important role in the complex regulatory mechanisms governing gene transcription, and their dysregulation can cause diseases such as cancer. The lack of methods for site-selectively modifying native chromatin, however, limits our understanding of the functional roles of a specific histone PTM, not as a single mark, but in the intertwined PTM network. Here, we report a synthetic catalyst DMAP-SH (DSH), which activates chemically stable thioesters (including acetyl-CoA) under physiological conditions and transfers various acyl groups to the proximate amino groups. Our data suggest that DSH, conjugated with a nucleosome ligand, such as pyrrole-imidazole-polyamide and LANA (latency-associated nuclear antigen)-peptide, promotes both natural (including acetylation, butyrylation, malonylation, and ubiquitination) and non-natural (azido- and phosphoryl labeling) PTMs on histones in recombinant nucleosomes and/or in native chromatin, at lysine residues close to the DSH moiety. To investigate the validity of our method, we used LANA-DSH to promote histone H2B lysine-120 (K120) acylation, the function of which is largely unknown. H2BK120 acetylation and malonylation modulated higher-order chromatin structures by reducing internucleosomal interactions, and this modulation was further enhanced by histone tail acetylation. This approach, therefore, may have versatile applications for dissecting the regulatory mechanisms underlying chromatin function.[1)]

1) *J. Am. Chem. Soc.* **2017**, *139*, 7568.