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Validation of epigenetic therapeutic target proteins for homogenous assay performance

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Results from sequencing large numbers of normal vs. tumor samples from the cancer genome atlas project (TCGA) revealed a great number of potential new therapeutic targets among epigenetic enzymes and factors. An outcome of this large scale project is that there is significant interest in developing screening strategies for many of the classes of these proteins, including histone deacetylases (HDACs), histone acetyltransferases (HATs), lysine methyltransferases (KMTs), lysine demethylases (KDMs), and bromodomain containing proteins (bromodomains). While the activity of some of these targets have yet to be validated using screening platforms that use peptide substrates (i.e. Perkin Elmer AlphaLISA), Active Motif has produced a protein toolbox of reagents including active enzymes, recombinant substrates, and detection antibodies for homogenous assay platforms such as AlphaLISA. We have validated reagents used in these assays for targets HDAC3, LSD1, p300, SETDB1, and BRD family members to ensure our ability to validate these proteins for performance in screening assays. As assessed by AlphaLISA assays, the IC50 values for various reference compounds for the enzymes under evaluation, are well within published results. The protein toolbox continues to expand to include a range of enzyme substrates, from peptides and recombinant histones bearing post-translational modifications to more complex, and biologically contextual recombinant octamers, oligonucleosomes, and "designer" mononucleosomes, which include site directed post-translational modifications. The expanding portfolio of substrates will enable screens of additional therapeutic targets using these higher order nucleosome substrates which may enable identification of small molecule compounds which exhibit greater specificity or selectively in vivo relative to those currently identified using peptide substrates.

Biography

Masato Yonezawa has nearly a total of ~20 years of experience in epigenetics research in academia and industries. Analyzed epigenetic phenomena by means of molecular biology and biochemistry. He is highly skilled with enzymatic assays and screened several inhibitors of chromatin modifying enzymes and would like to contribute to epigenetic research and therapy by developing useful tools and drugs.

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