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The design and utilization of the scintillation proximity assay to screen for p300 inhibitors

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Histone acetyltransferases (HATs) mediate the transfer of an acetyl group from the cofactor, acetyl-CoA, to the ε-amino group of specific lysines in diverse protein substrates, most notably nuclear histones. The deregulation of these enzymes are connected to a number of disease, such as prostate and breast cancer; however to date, there are no FDA approved drug targeting HATs. Reliable and rapid biochemical assays for HATs are critical for understanding biological functions of protein acetylation, as well as for screening small-molecule inhibitors and activators of HAT enzymes. We present the design of a scintillation proximity assay (SPA) which was used in an inhibitor library screening. The acetyl donor was [3H]Ac-CoA and a biotin-modified histone peptide served as the HAT substrate. Following the HAT reaction, guanidinium chloride was added to quench the reaction. Lastly, streptavidin-coated beads were added to induce proximity of acetylated substrate to the scintillant molecules. Overall, this microplate formatted, mix-and-measure assay showed consistent and robust performance for HAT activity measurement. The SPA was used in a p300 inhibitor screening with compounds identified from a computational screening. A few hits were identified from the p300 inhibitor screening with IC50 values in the submicromolar range. Surprisingly, when the best p300 inhibitor hits were counter screened with other HAT family members, a GCN5 activator was identified. This novel activator compound increased GCN5 activity by four-fold.

Biography

Liza Ngo has completed her Master's degree from the Georgia State University. She is currently pursuing PhD in the Pharmaceutical Biomedical Science Department at the University of Georgia. She was awarded with the National Science Foundation Graduate Fellowship.

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