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Evaluating drug-chromatin interactions using novel methods for target engagement studies

Marta Rucka
Promega, UK

Regulation of gene expression is a dynamic process orchestrated and maintained by a large variety of chromatin-interacting proteins. Understanding these chromatin-protein complexes and their binding kinetics is crucial for development of the small-molecule drugs. Promega has developed NanoBRET™ technology, which allows for dynamic measurement of protein:protein interactions (PPIs) in living cells. This proximity-based assay measures energy transfer from a bioluminescent protein donor (NanoLuc® fusion protein) to a fluorescent protein acceptor (HaloTag® fusion protein) under physiological conditions. Furthermore, the assessment of chromatin-protein interaction reversibility is also possible allowing for identification of compounds that either induce or inhibit the target complex. Evaluating the engagement of these small molecules with chromatin regulatory proteins provides useful information for chemical probe optimization and further pharmaceutical development. In addition to the specificity and affinity of target engagement, binding dynamics under non-equilibrium conditions may also underlie the therapeutic potential of the drugs. Promega has developed NanoBRET™ Target Engagement system, wherein the apparent binding affinity and permeability of test compound is measured by competitive displacement of a broad-coverage NanoBRET™ Tracer reversibly bound to a NanoLuc fusion protein in cells. As both the compound and tracer compete directly for the same binding site it enables quantification of drug residence time on the targets. During this talk the author will discuss the work they have completed using histone deacetylases (HDACs) and bromodomain (BRD)-containing proteins as the targets in our NanoBRET PPI and target engagement studies.

Recent Publications

1. Machleidt et al. (2015) NanoBRET ¬– A novel BRET platform for the analysis of protein-protein interactions. ACS Chem Biol. 10(8):1797-804.
2. Roberts et al. (2015) Target engagement and drug residence time can be observed in living cells with BRET. Nat Commun. 6:10091.
3. Warning et al. (2016) Potent and selective bivalent inhibitors of BET bromodomains. Nat Chem Biol. 12(12):1097-1104.

Biography

Marta Rucka received a PhD from University of Southampton in 2014. Her PhD and Postdoctoral research focused on dissecting the role of transcriptional co-repressors in the regulation of tumour cell motility. Currently, she looks after cellular analysis and proteomics portfolio at Promega UK. Promega continues to develop novel and exciting methods designed to enhance drug discovery and life science research, including NanoLuc-based technology for direct assessment of target engagement and residence time in live cells.