Panagis Filippakopoulos

Department of Clinical Medicine, Structural Genomics Consortium & Ludwig Institute for Cancer Research, University of Oxford, Old Road Campus, Roosevelt Drive, Oxford OX3 7DQ, UK

Targeting the Epigenetic Readout of Acetyl-Lysine

Lysine acetylation has emerged as a signalling modification of broad relevance to cellular and disease biology. Targeting the enzymes which reversibly mediate side-chain acetylation has been an active area of drug discovery research for many years. To date, successful efforts have been limited to the “erasers” (histone deacetylases) of covalent modifications arising in the context of nuclear chromatin. Bromodomains (BRDs) are evolutionary conserved protein interaction modules that specifically recognize ε-N-lysine acetylation (K_{ac}) motifs (“readers”), a key event in the reading process of epigenetic marks. They are of substantial biological interest, as components of transcription factor complexes and determinants of epigenetic memory. Importantly, inhibition of their ability to read K_{ac} is possible: the Bromo and Extra Terminal (BET) sub family has recently been successfully targeted by several classes of small molecule inhibitors leading to pan-BET inhibitors that are capable of attenuating BET function. BET proteins have a modular architecture, including two N-terminal BRD modules and an extra terminal (ET) domain. They recognize and bind to patterns of lysine acetylation found on histones and further act to recruit components of the transcriptional machinery via their modular architecture. Inhibition of their K_{ac} readout function results in dissociation from chromatin, thus controlling the transcription of key oncogenes and anti-apoptotic proteins. With several chemical scaffolds on track in clinical trials, there is a need to generate well characterized, highly specific, potent and cell permeable chemical tools that can be used to validate the underlying biology of these protein targets in order to successfully target them in diverse clinical settings.