Design, Synthesis and Biological Characterization of Potent and Selective Molecular Probes for the CREBBP Bromodomain

V. Pascanu[1], A. Dolbois[1], A. Caflisch[1]*, C. Nevado[1]*

[1]University of Zurich

The ε-*N*-acetylation of lysine residues on histone tails is one of the most prevalent post-translational modifications. Bromodomains are protein modules (*ca.* 110 amino acids) that specifically recognize (read) these acetylated marks, mediating protein-protein interactions and their downstream biological function. Therefore, bromodomains are interesting targets for "reprogramming" the epigenome with the potential to access a previously unexplored therapeutic space.[1] Out of 61 different bromodomains identified in humans, BRD4(1) and the BET family have been the most investigated so far, leading to inhibitors already in phase II of clinical trials.[2] In sharp contrast, the biological relevance of other bromodomains, like the CREBBP/EP300, remains unclear.

Originating from an in-silico fragment–based approach, our group has successfully designed, synthesized and biologically characterized a series of acetylbenzene derivatives as potent and selective CREBBP ligands.[3] Based on the information obtained from the X-Ray structure of the parent compound in complex with CREBBP, compounds with improved potency and unprecedented selectivity against BRD4(1) have been identified. These compounds have been further optimized in terms of solubility, cell permeability and PK/PD properties. Furthermore our lead compound has been tagged with a fluorescent probe that facilitates its study in relevant *in vivo* models. This represents a valuable tool for understanding the biological consequences of CREBBP misregulation.

[1]Muller, S.; Filippakopoulos, P.; Knapp, S. *Expert Rev. Mol. Med.*, **2011**, 13, e29.
[2] Filippakopoulos, P.; Knapp, S. *Nat. Rev. Drug Discov.*, **2014**, 13, 337-356.
[3] a) Unzue, A.; Xu, M.; Dong, J.; Wiedmer, L.; Spiliotopoulos, D.; Caflisch, A.; Nevado, C. *J. Med. Chem.*, **2016**, 59, 1350-1356. b) Xu, M.; Unzue, A.; Dong, J.; Spiliotopoulos, D.; Nevado, C.; Caflisch, A. *J. Med. Chem.*, **2016**, 59, 1340-1349. c) Unzue, A.; Zhao, H.; Lolli, G.; Dong, J.; Zhu, J.; Zechner, M.; Dolbois, A.; Caflisch, A.; Nevado, C. *J. Med. Chem.*, **2016**, 59, 3087-3097.