Poster Presentation

MS53.P18

Virtual Screening of Histone Lysine Demethylase(JMJD2) identifies new inhibitors

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The JmjC domain-containing proteins are hydroxylases that confer posttranslational modifications on histone tails, by removing methylation marks on methylated lysine residues. This serves to either promote or repress gene transcription. The JMJD2A-D family members include the enzyme Jumonji domain 2C (JMJD2C), which specifically demethylates di- and trimethylated histone H3 at Lys 9 or Lys 36.[1] Dysregulation of JMJD2C has been implicated in prostate, colonic, and breast cancer as the demethylase can modify the expression levels of oncogenes.[2] The goal of the present study was to identify potent and selective small-molecule inhibitors of JMJD2C, to be used as chemical biology tools to further investigate the role of JMJD2C in cell proliferation and survival. Using high-resolution crystal structures of the JMJD2 subfamily members as templates, we have performed a small molecule virtual docking screen. From the ~3 million molecules that were docked, this experiment identified 21 compounds as possible leads. These compounds were tested against JMJD2C in enzymatic assays and here we report an overall hit rate of 76%, with 8 compounds demonstrating an IC50 of 176µM to 1.18µM. A molecule containing a salicylate core was selected as a candidate for optimization and thus far we have completed several rounds of iterative target-specific compound docking, hybrid molecule design, compound synthesis and in vitro characterization. Notably, our method demonstrated a substantial increase in potency when we linked two docked fragments together and further derivatized this new scaffold, through which we have successfully derived a 65nM inhibitor of JMJD2C. A compound representing the inhibitor scaffold has been co-crystallized with JMJD2A to a resolution of 2.4 Å. In the crystal structure each asymmetric unit contains two JMJD2A monomers, each bound to a single inhibitor molecule. This complex-structure superposes well with the docked pose for the hybrid series of compounds. We are now focusing our efforts on identifying an inhibitor that is selective for the JMJD2 family over other JmjC domain-containing proteins.

[1] *D.D. Le, D.G. Fujimori. Current opinion in chemical biology. 2012, 16(5-6), 507–515,* ***[2]*** *R.M. Labbé, A. Holowatyj , Z. Yan. Am J Transl Res 2014, 6(1), 1-15*

Keywords: structure based design, virtual screening docking, histone lysine demethylase