Pick an isoform: Selective Inhibition of JmjC Histone Demethylases

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http://www.pharmacy.nus.edu.sg/staff/phaewcy/Project%201.html

Methylation of histone lysine residue can result in either gene activation or gene silencing, depending on the position of the lysine, its methylation state and the presence of other modifications. These epigenetic marks are reversible and may be removed by histone demethylases; the largest family being the JmjC enzymes, which employ 2-oxoglutarate (2OG) as a cosubstrate. Importantly, dysregulation of these JmjC demethylases provides the mechanism to many of the human diseases, such as cancer, metabolic disorders and neurodegenerative diseases. There are 5 JmjC demethylase subfamilies, targeting histone lysines at H3K4, H3K9, H3K27, and H3K36; each of these JmjC enzymes displays remarkable sequence and methylation-state specificity.

One of the challenges in achieving selective inhibition of the JmjC histone demethylases is their structural similarities, especially within the catalytic domain. We have provided proof of principle that selective inhibition of JmjC subfamilies and isoform subgroups is achievable through linking of both 2-oxoglutarate (2OG) and substrate binding sites. By exploiting the inherent substrate selectivity of the JmjC enzymes, compound that are either subfamily selective or isoform-subgroup selective could also be achieved. The results should provide a basis for the development of potent and selective JmjC inhibitors, possibly suitable for clinical use.

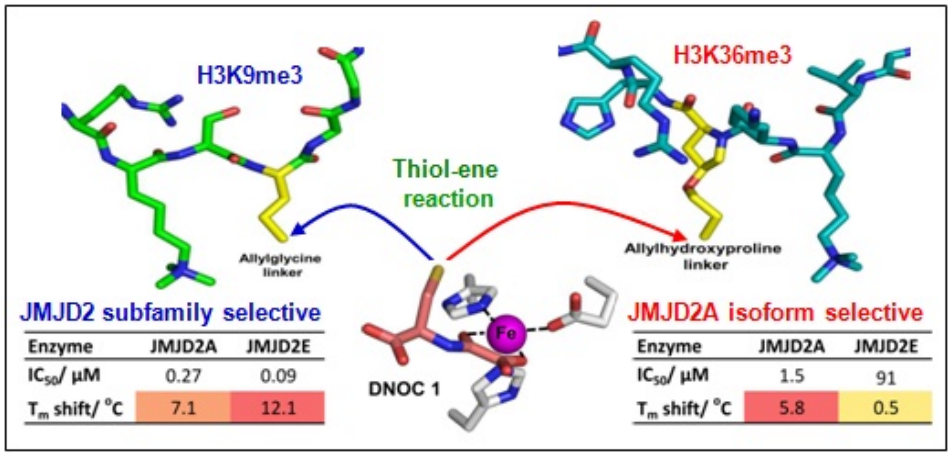

Figure 1. Compound based on H3K9me3 exhibits a high degree of selectivity and potency for the JMJD2 over other subfamily members while that based on H3K36me3 is selective for JMJD2A over JMJD2E.