# Structure-Based Design of Histone Demethylase Inhibitors

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The genetic information in eukaryotic cells is organised in a specific structure called chromatin. The basic unit of chromatin is the nucleosome, which consists of four histone proteins and ~147 bp of DNA. [1] There are different types of histones known, and the N-terminal tails of these proteins contain sites for post-translational modifications directly linked to gene expression. The modificatons include phosporylation, acetylation, ubiquitinylation, methylation sumoylation and ribosylation. Each modification is mediated by specific enzymes. LSD1 (Lysine Specific Demethylase 1) is one of the histone demethylases which removes one methyl group from methylated lysine residues. Lysine demethylation may have a dual role in genetic expression: gene repression (H3K4) and gene activation (H3K9). [2]

It has recently been demonstrated that the androgen receptor (AR)-LSD1 complex demethylates a repressive histone mark (H3K9) and then promote genes activation. [3] Experimental data show, also, that LSD1 is strongly expressed in prostate cancers with high a Gleason score. [4] For these reasons, specifics modulation of LSD1 activity might be a promising therapeutic strategy in tissues where AR has a key physiological role.

LSD1 is a flavin-dependent amine oxidase which shares sequence identity with other flavin-dependent amine oxidases like monoamine oxidase (MAO), and polyamine oxidase (PAO). First, we visually inspected differences and similarities of the active sites among these enzymes. Next, several docking studies were evaluated using the available crystal structures of LSD1 and the related oxidases. For the evaluation studies we selected different ligand data sets comprising reported MAO and PAO inhibitors. The docking setup which showed the best accuracy and enrichment factors was selected for virtual screening of LSD1 inhibitors. Preliminary biological data were obtained and will be discussed in the context of the target structure.

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