# Epigenetics – Histone Deacetylase (HDAC) and Sirtuin Inhibitors

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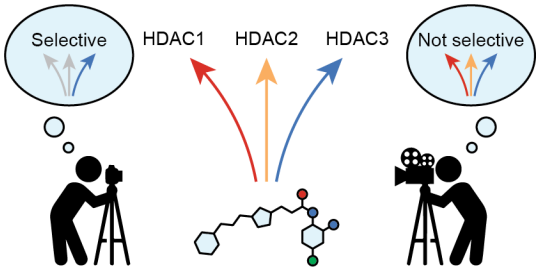
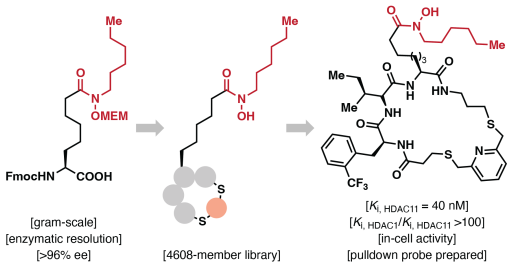
Epigenetic mechanisms are important for temporal and tissue-specific regulation of DNA transcription in our different cell types. An example of an epigenetic modification is acetylation of the e-amino groups of lysine residues in histone proteins. Histones are the proteins onto which our DNA is packaged in the cell nuclei. Therefore, DNA transcription is indirectly affected by the extent of acetylation, and thus, modulation of the activities of the enzymes that regulate this acetylation is a powerful way of affecting transcription.
Inhibition of HDAC enzymes have proven to have potential in cancer treatment, and four compounds targeting HDACs have been approved by the FDA thus far.

**Aims:** In the Olsen group, we explore several avenues towards inhibition of HDAC and sirtuin enzymes with the aim of developing novel chemical probes and degraders against the 18 different human isozymes. We explore both novel chemical functionalities with potential to bind in the enzyme catalytic site, as well as more elaborate cyclic peptide-based structures that interact with the protein surface.




**Methodology and approach:** The projects in the laboratory within this area will involve design, synthesis, and enzymological evaluation of novel inhibitors. The M.Sc. student will, among other techniques, be performing solution- and solid-phase synthesis, compound characterization by HPLC, MS, and NMR, as well as enzymatic inhibition assays and cell-based assays.

**Selected references:**


D. Danková, et al. Discovery of de novo Macrocyclic Inhibitors of Histone Deacetylase 11. *JACS Au* **2025**, *5*, 1299–1307. PDF [ChemRxiv]

T. N. Hansen, et al. SuFEx-Based Solid-Phase Synthesis of Compound Arrays: Discovery of Histone Deacetylase Inhibitors. *JACS Au* **2024**, *4*, 1854–1862. PDF [ChemRxiv]

N. Rajabi,[+] T. N. Hansen,[+] A. L. Nielsen,[+] et al.. Investigation of Carboxylic Acid Isosteres and Prodrugs for Inhibition of the Human SIRT5 Lysine Deacylase Enzyme. *Angew. Chem. Int. Ed.* **2022**, *61*, e202115805. PDF [ChemRxiv] *(Hot Paper)*

For more information, please visit our lab website (https://drug.ku.dk/olsen-lab/) contact Prof. Christian A. Olsen (cao@sund.ku.dk) directly.