Epigenetics 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 ε-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.

Interestingly, inhibition of HDAC enzymes have proven to have potential in cancer treatment, and four compounds targeting HDACs have been approved by the United States Food and Drug Administration thus far.

In the Olsen group, we explore several avenues towards inhibition of HDAC enzymes with the aim of developing novel chemical entities with improved selectivity profiles across the class of eleven different HDAC isoforms. We explore both novel chemical functionalities with potential to bind the Zn$^{2+}$ ion present in the enzyme catalytic site,[1] as well as more elaborate cyclic peptide-based structures that interact with the HDAC protein surface.[2,3] The projects in the laboratory within this area will involve design, synthesis, and enzymological evaluation of novel HDAC inhibitors. The M.Sc. student will, among other techniques, be performing solution- and solid-phase synthesis as well as enzymatic inhibition assays and enzyme kinetics.

The figure shows examples of cyclic peptide HDAC inhibitors (left) and an NMR structure with structure-activity relationship findings added (right).

