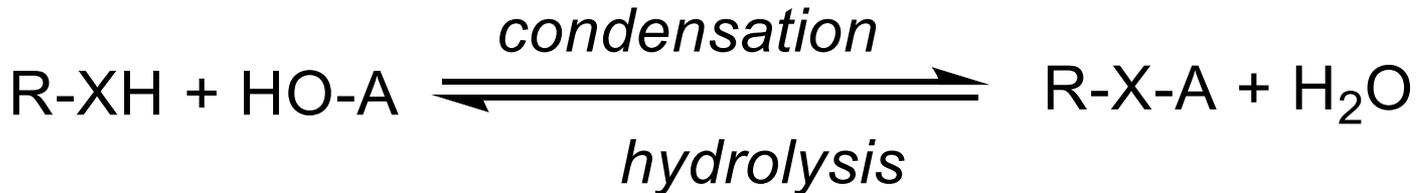


# Zn<sup>2+</sup> as a Lewis acid



The hydroxide ion bound to zinc, [Zn-OH]<sup>+</sup>, is a weaker nucleophile compared to free OH<sup>-</sup>, but definitely stronger than H<sub>2</sub>O and much more abundant than OH<sup>-</sup> at physiological pH.



*peptidase, lactamase, collagenase*



*esterase*

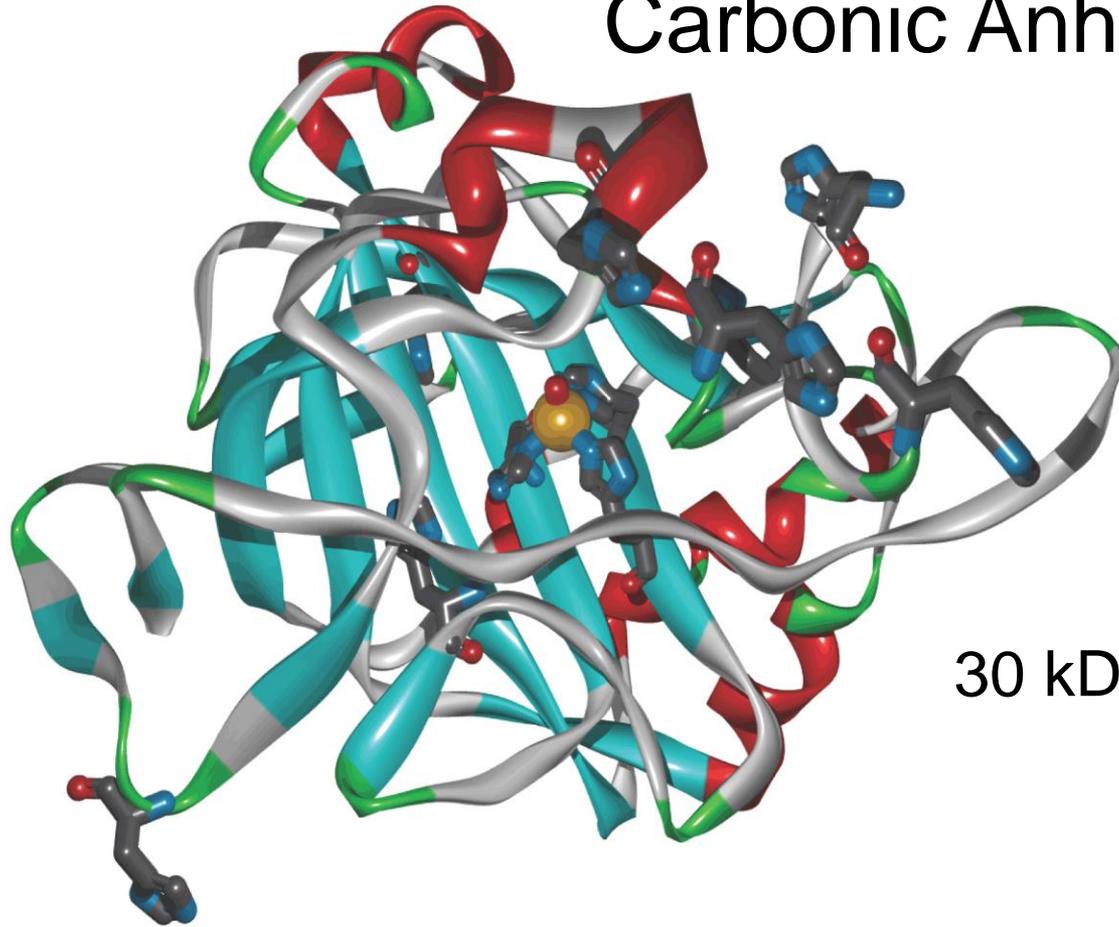


*phosphatase, nuclease*

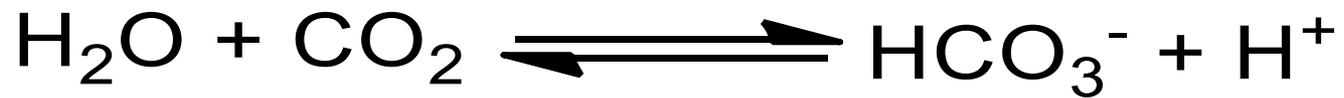
# Main features of biological zinc

- Exclusively as  $\text{Zn}^{2+}$
- $d^{10}$  (no LFSE)
- Flexible coordination number and geometry
- Catalytic (as Lewis acid) or structural role
- More than 200 Zn-proteins known (*zincosome*)

# Carbonic Anhydrase

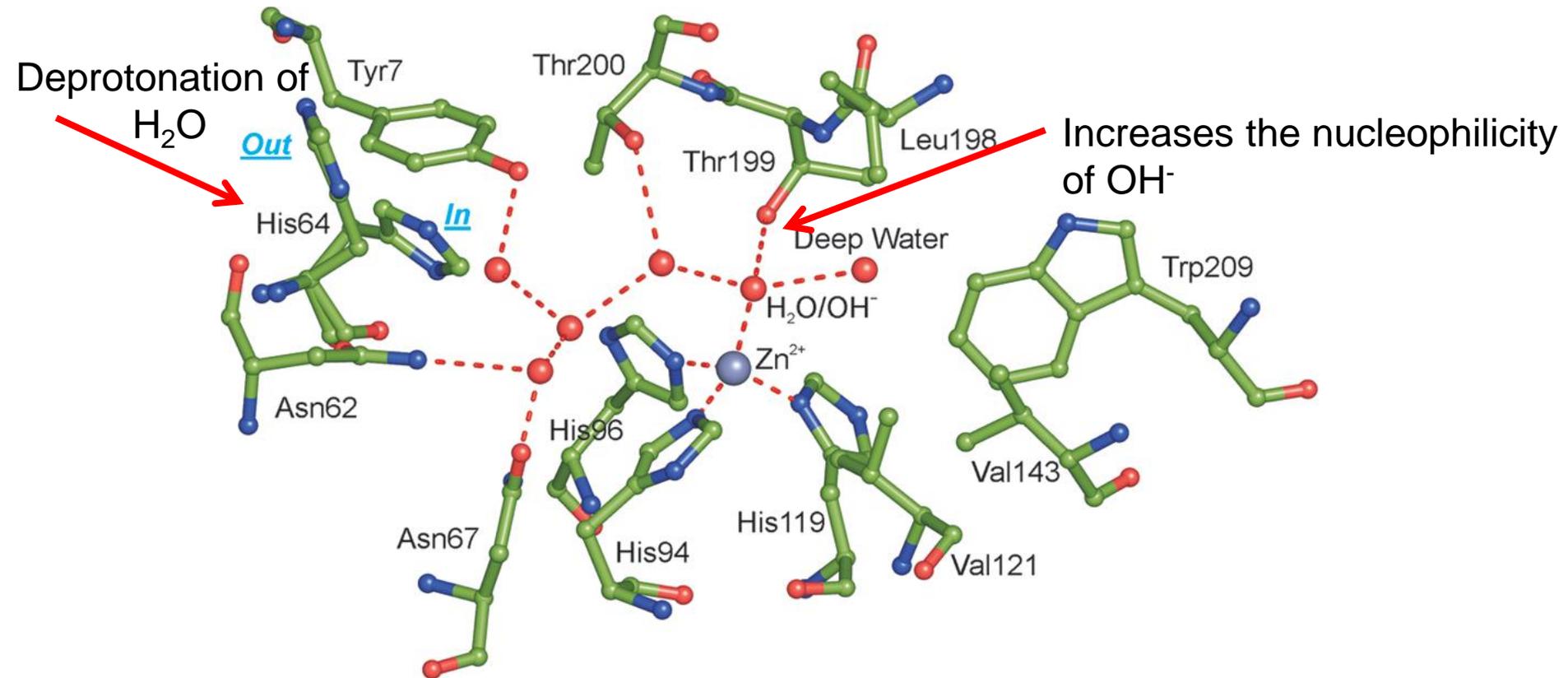
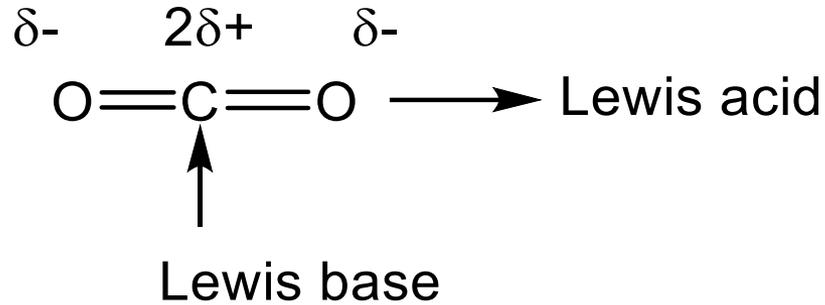


30 kDa, 259 a.a.

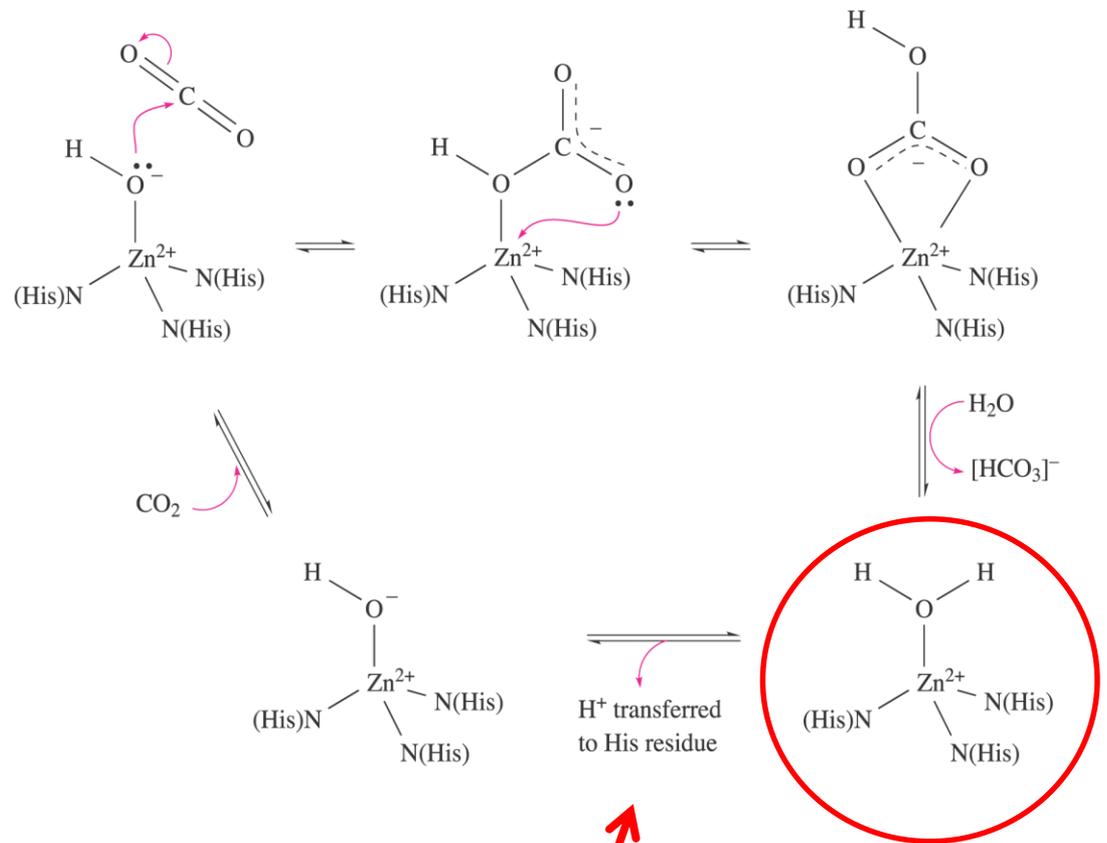
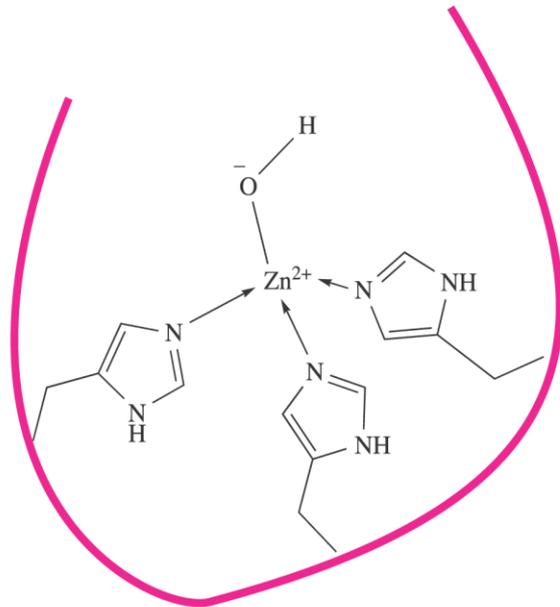


$$k \approx 10^{-1} \text{ s}^{-1} \rightarrow 10^6 \text{ s}^{-1}$$

# Catalytic site of carbonic anhydrase



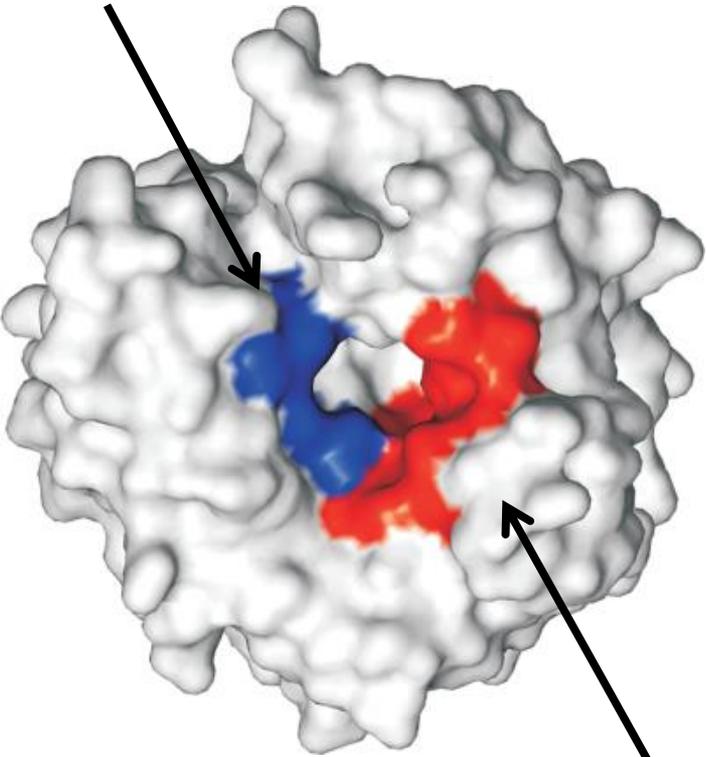
# Catalytic cycle of carbonic anhydrase



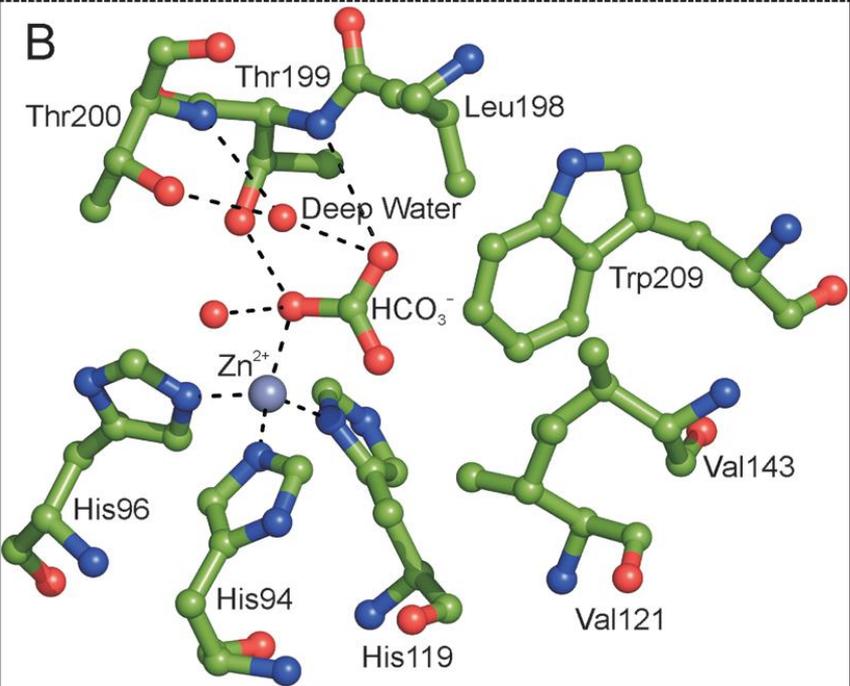
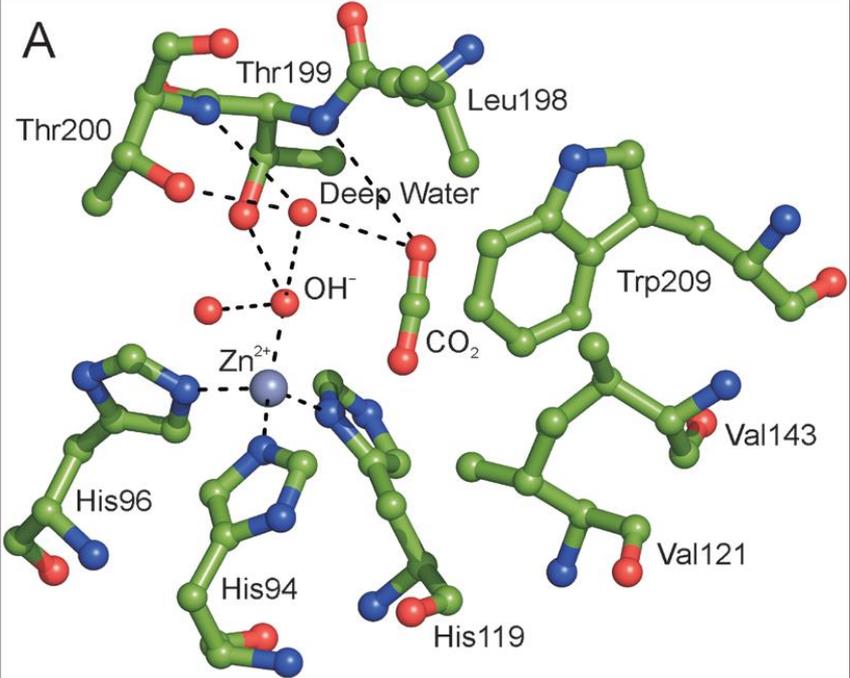
*Rate limiting*

# Catalytic cleft in CA

Hydrophilic region

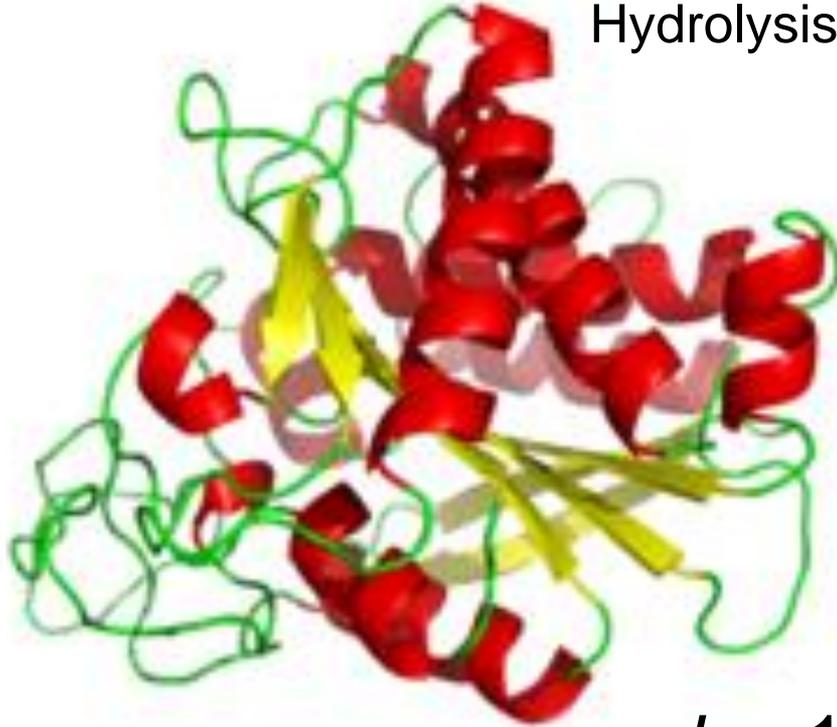


Hydrophobic region



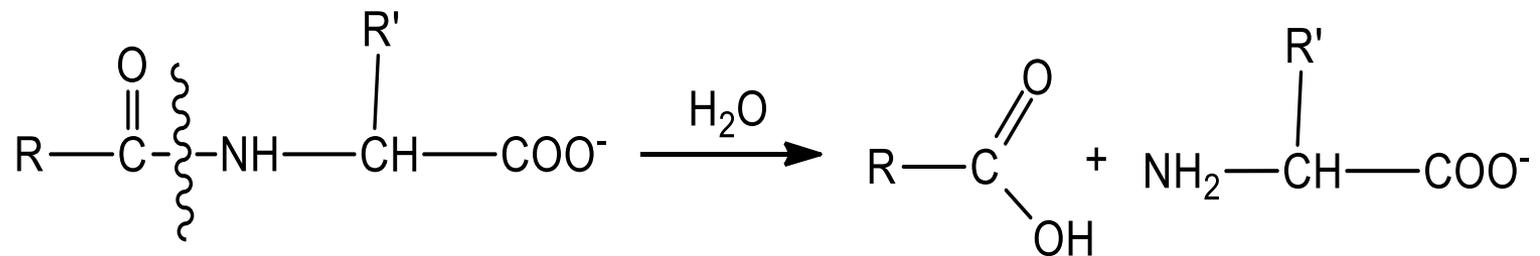
# Carboxypeptidase A (CPD A)

Hydrolysis of C-terminal aminoacids

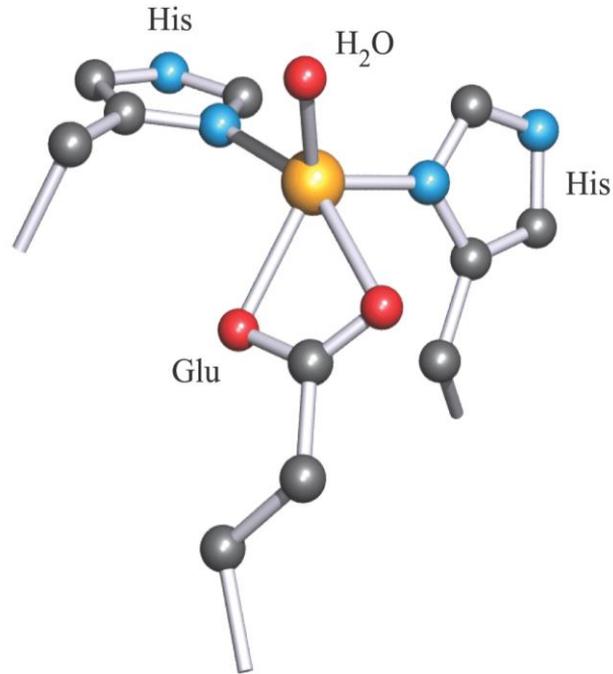


34 kDa, 300 a.a.

$$k \approx 10^{-11} \text{ s}^{-1} \rightarrow 10^4 \text{ s}^{-1}$$

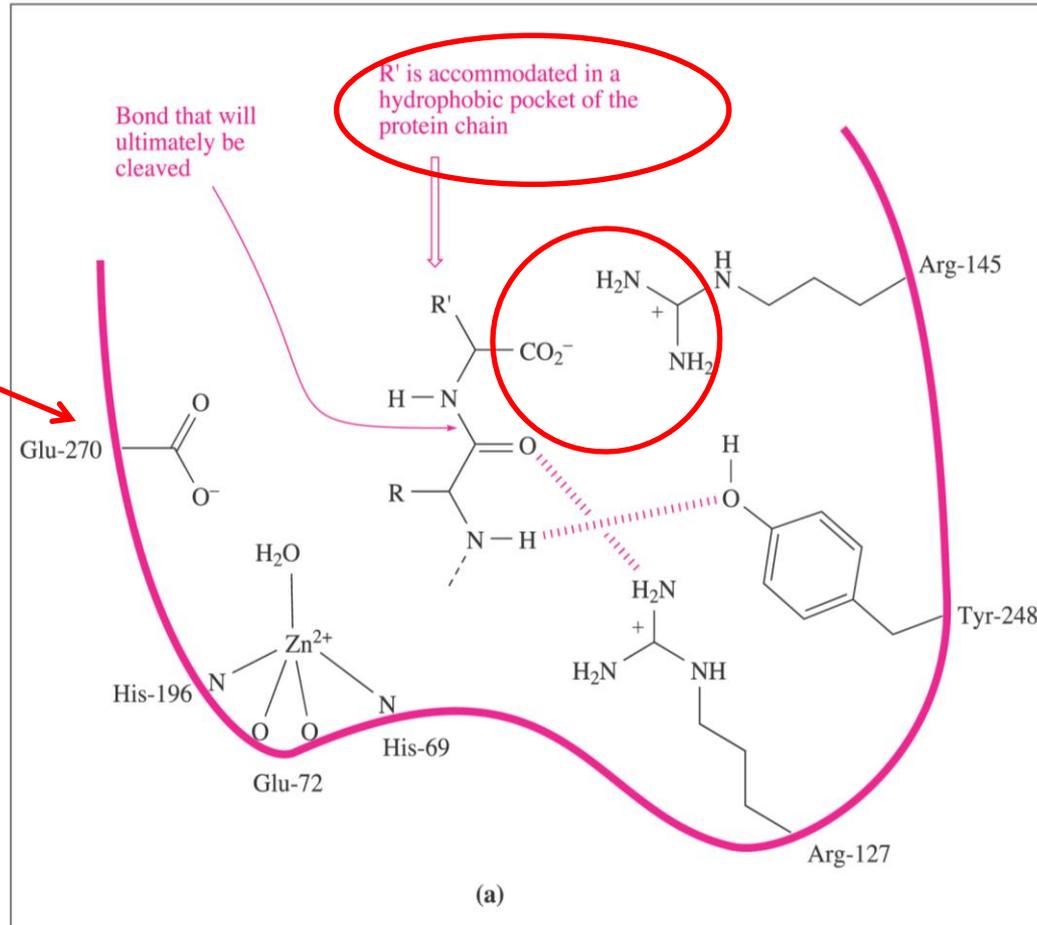


# Active site in CPD A

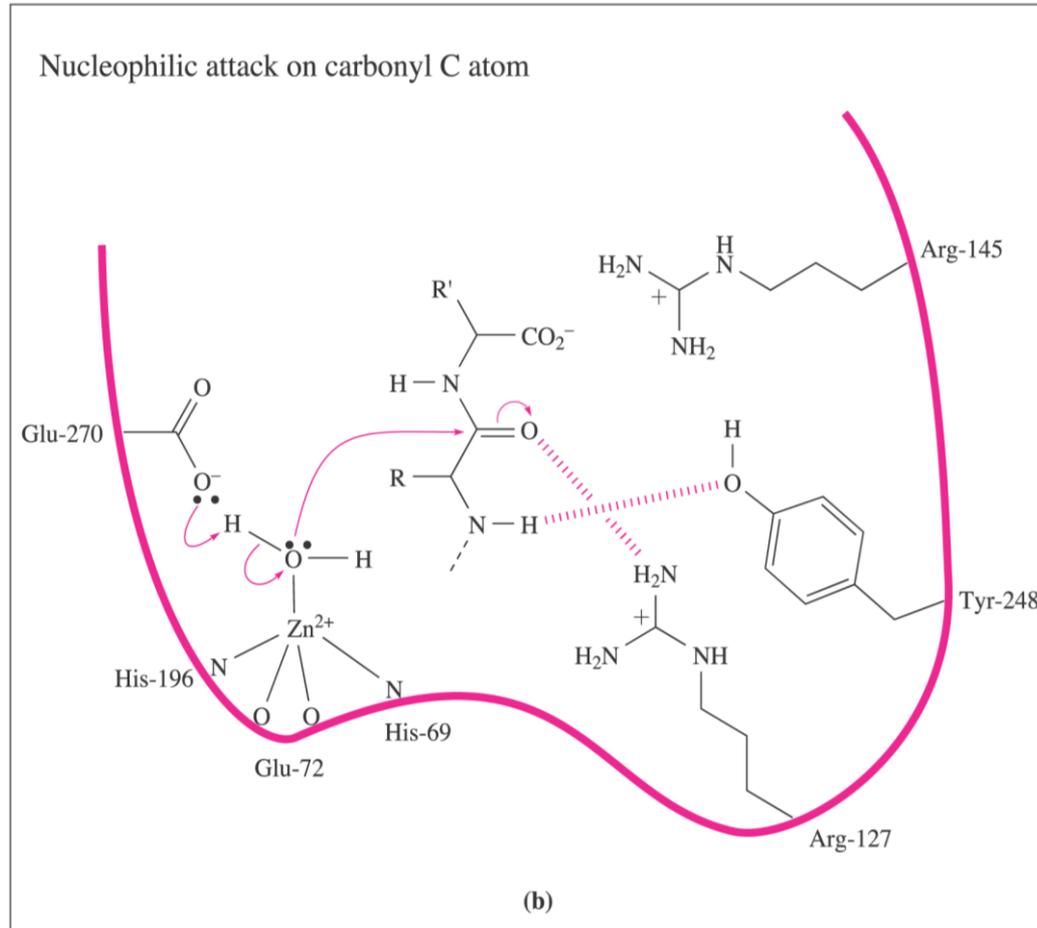


Carboxypeptidase A (CPD A, bovine)

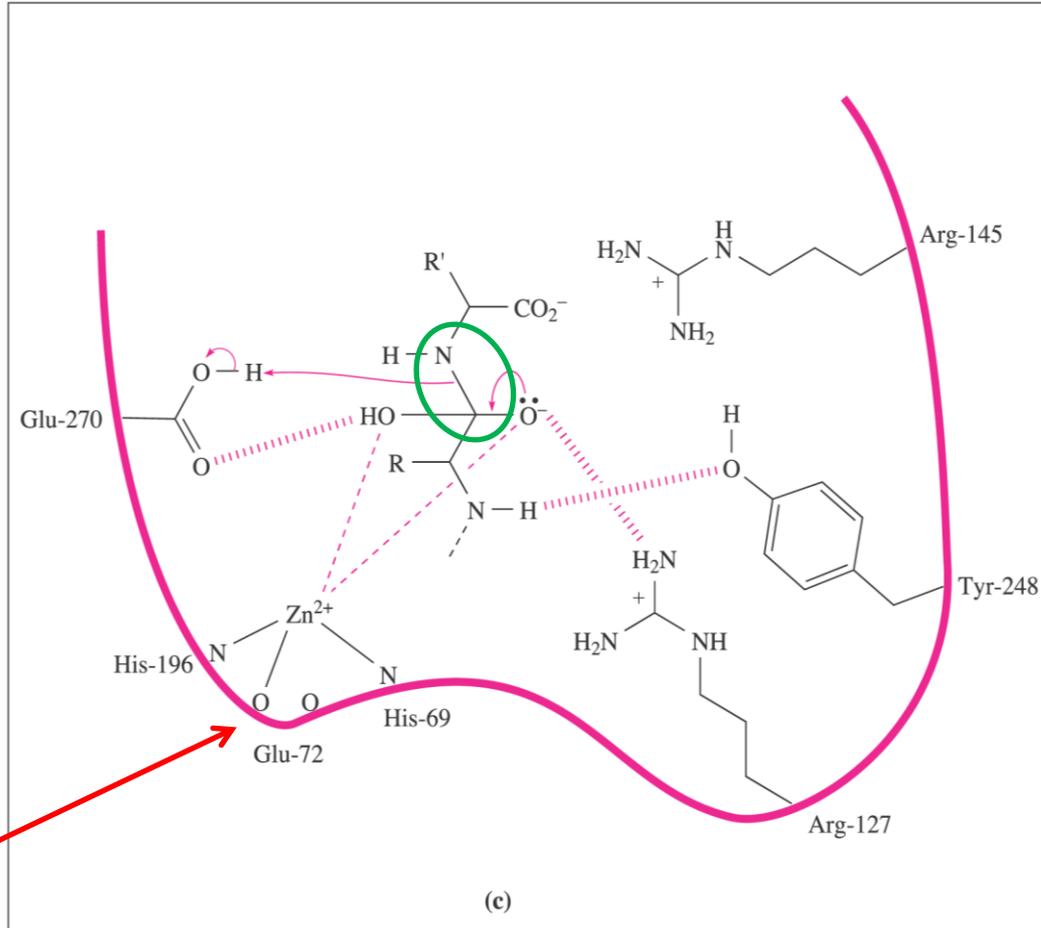
# Positioning of the substrate close to the active site of CPA



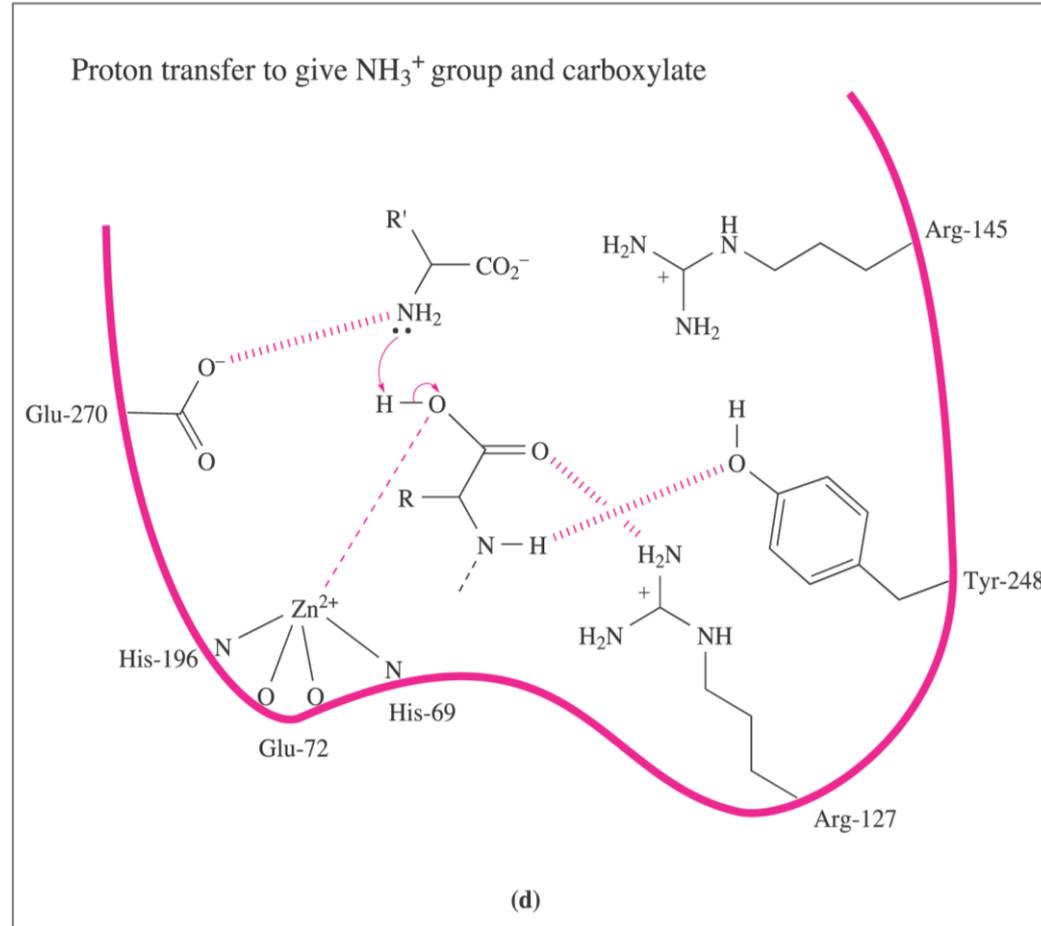
# Deprotonation of water molecule and nucleophilic attack



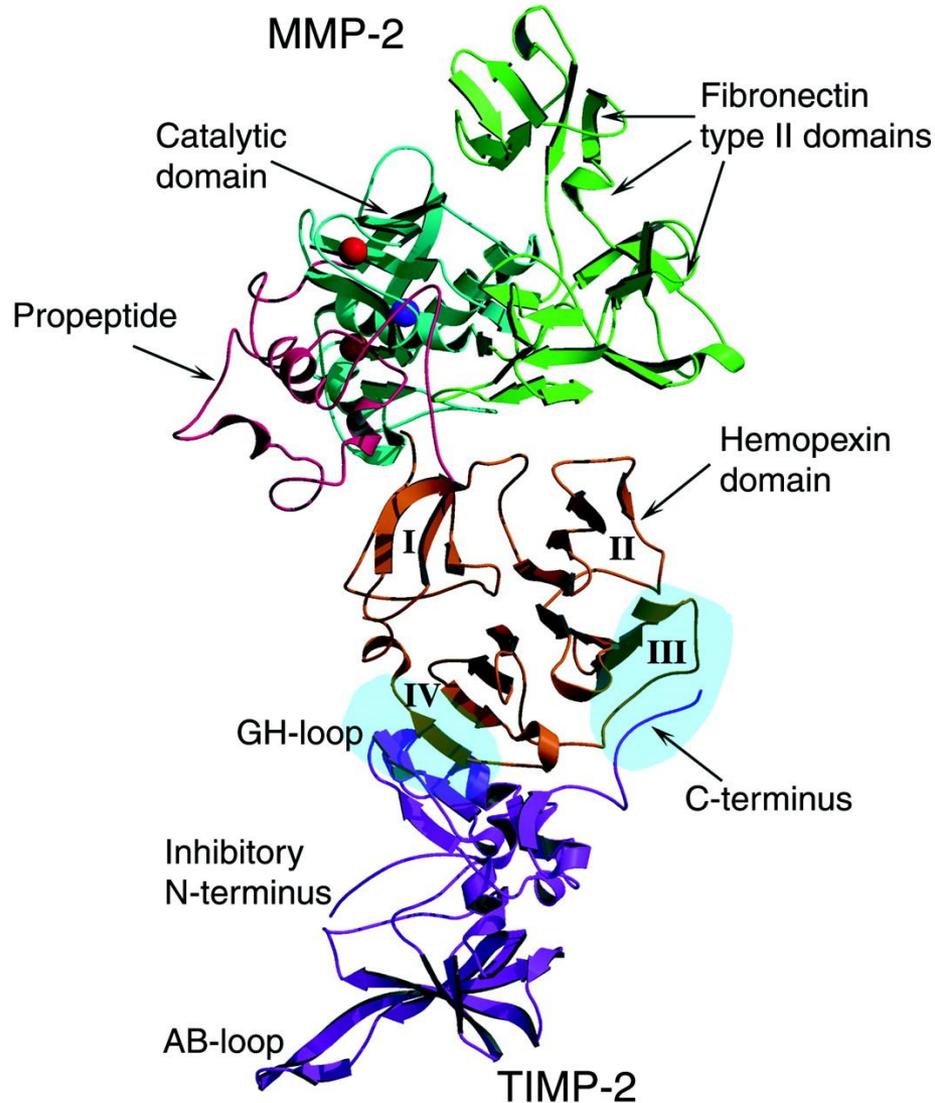
# Cleavage of the C–N peptidic bond



# Proton transfer with formation of the $\text{NH}_3^+$ and $\text{COO}^-$ groups



# Matrix MetalloProteinases (MMPs) + Tissue Inhibitors of MetalloProteinases (TIMPs)

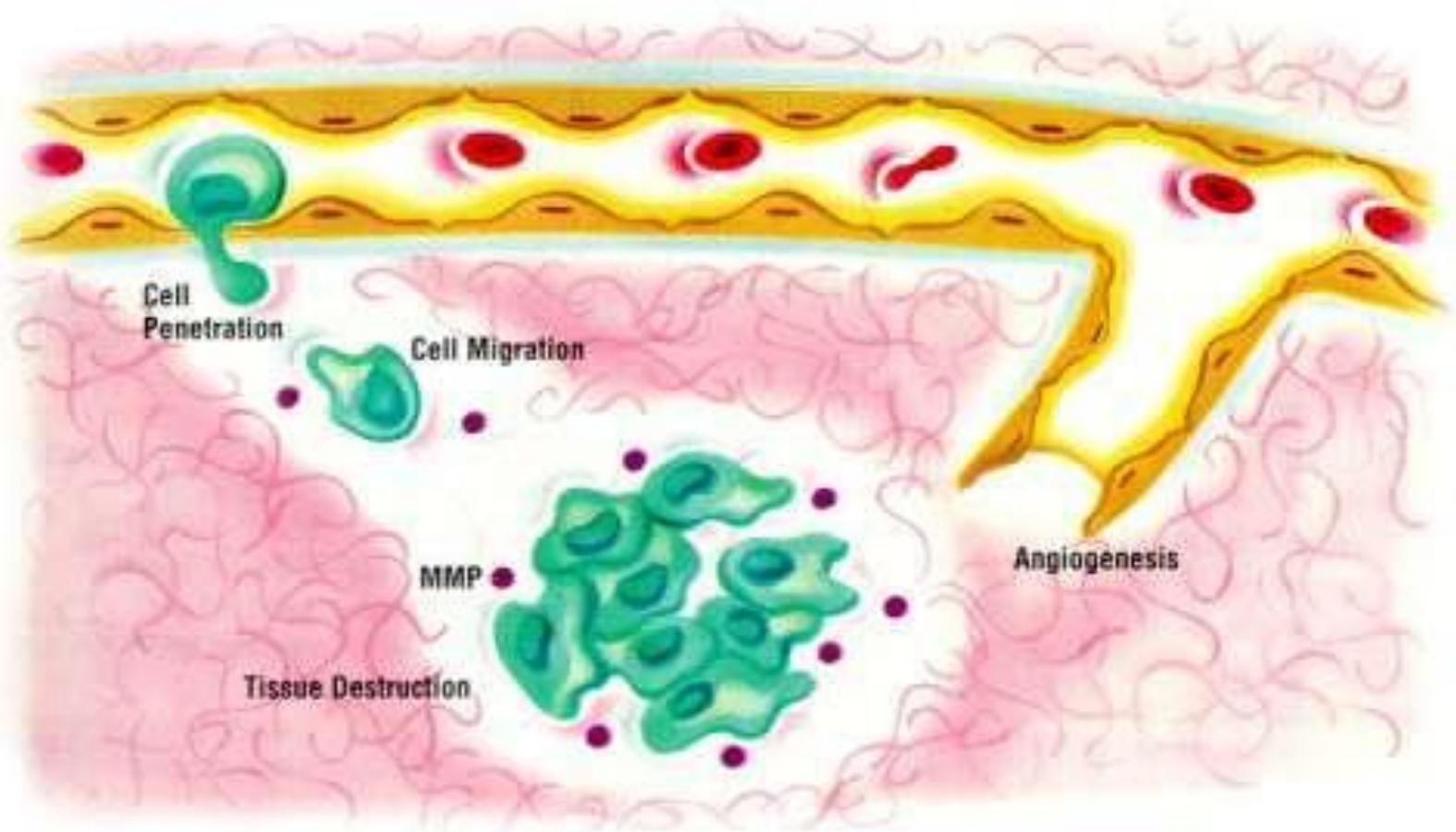


● = Zn

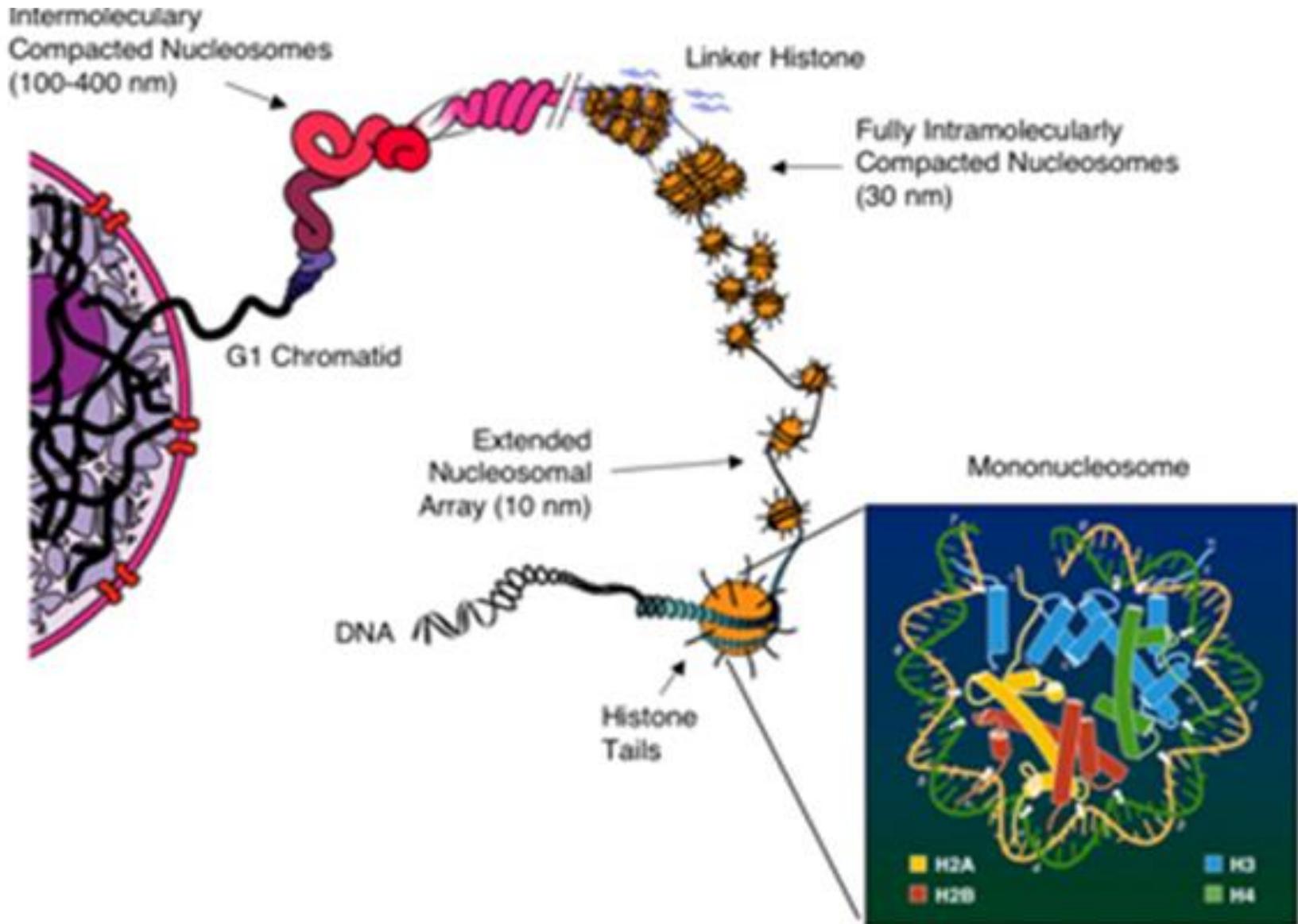
● = Ca

Zinc-endopeptidases that degrade the proteins constituting the extracellular matrices (e.g. collagen)

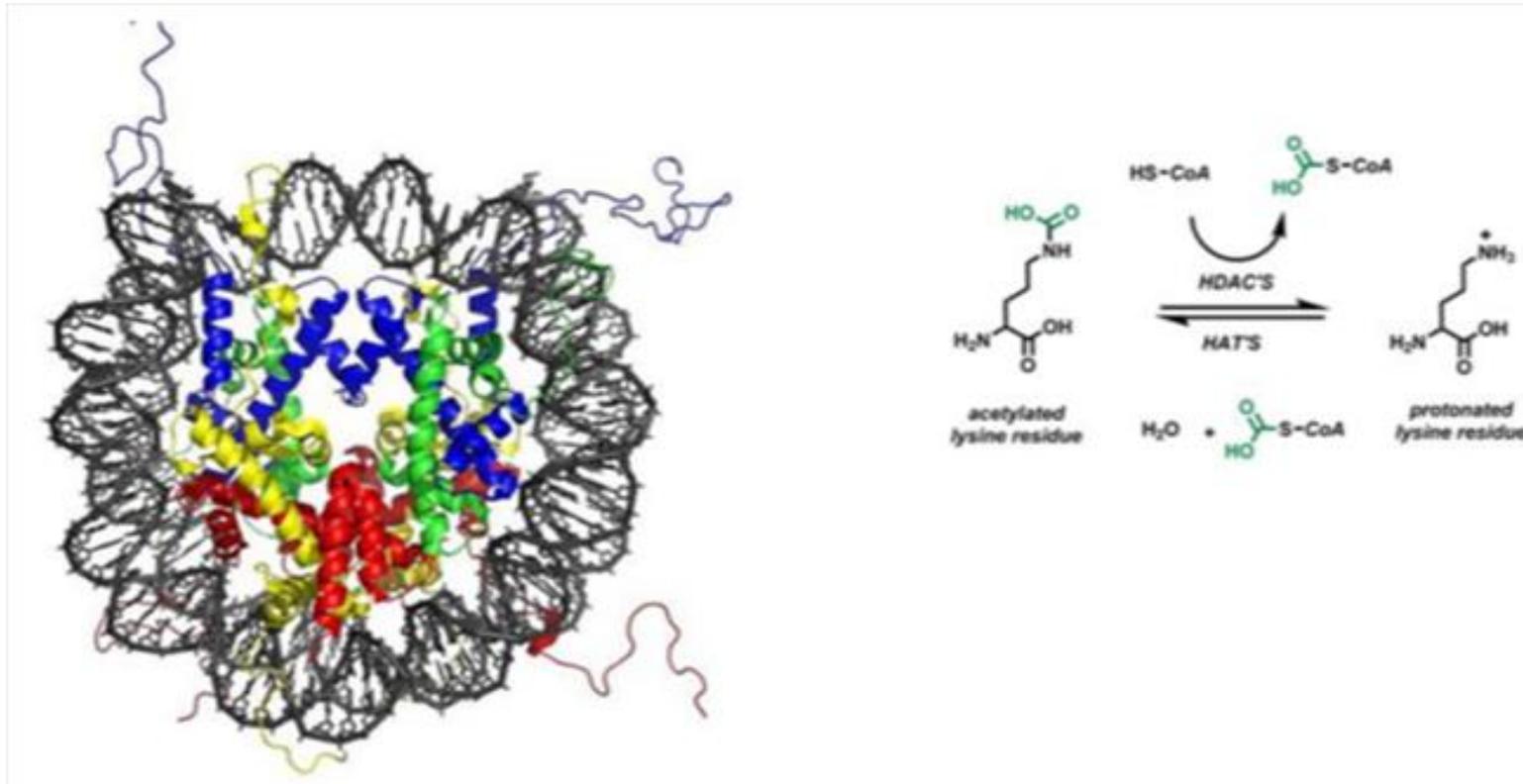
# Metastatic process facilitated by MMP



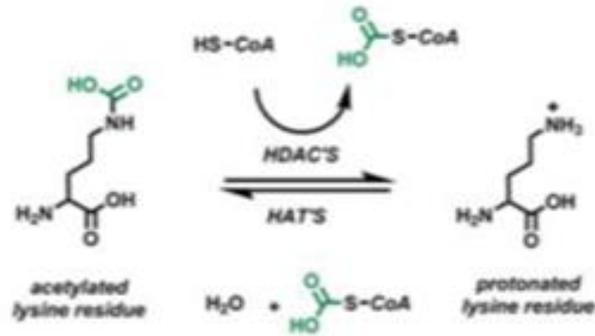
# Chromatin, Nucleosomes and Histones



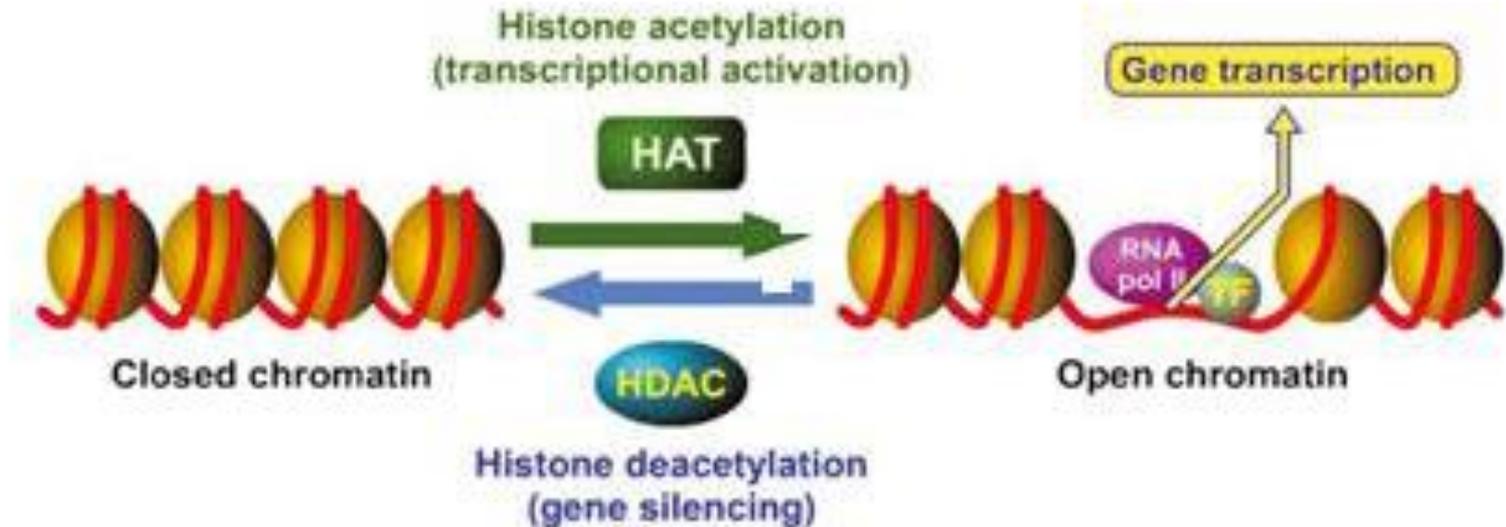
# Histone deacetylase (HDAC) and Histone acetyltransferase (HAT)



Nucleosome and Histones

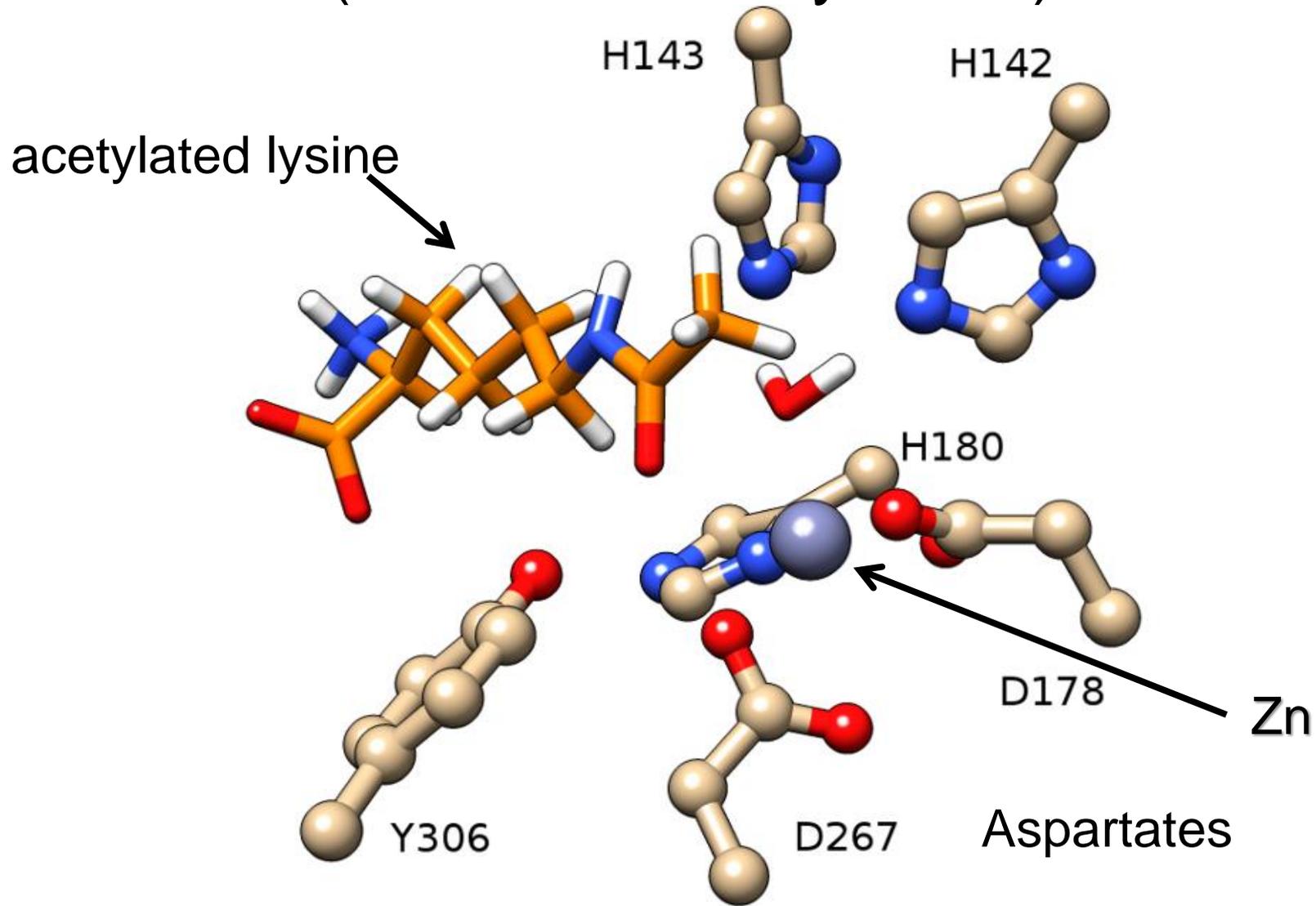


## acetylation and deacetylation of histone lysins

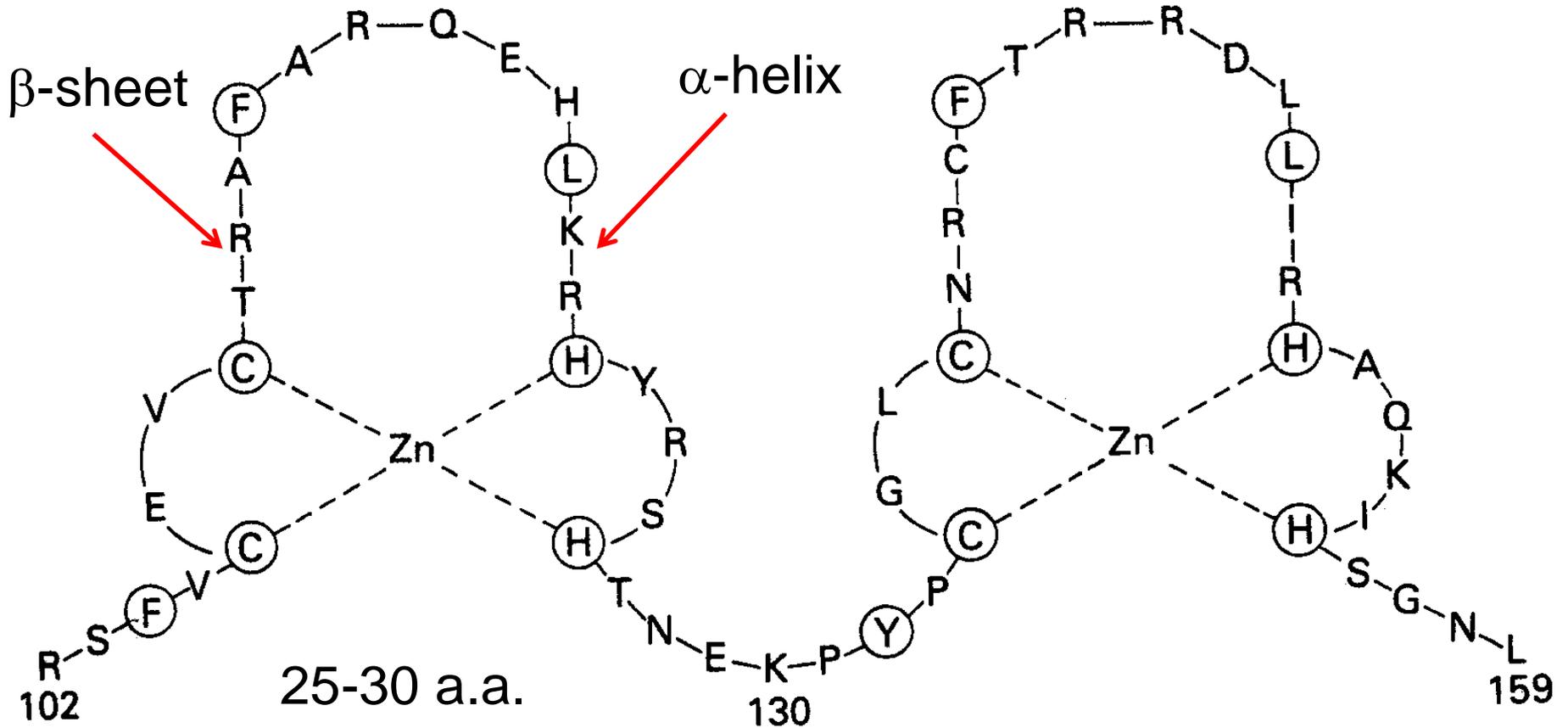


*epigenetic modulation*

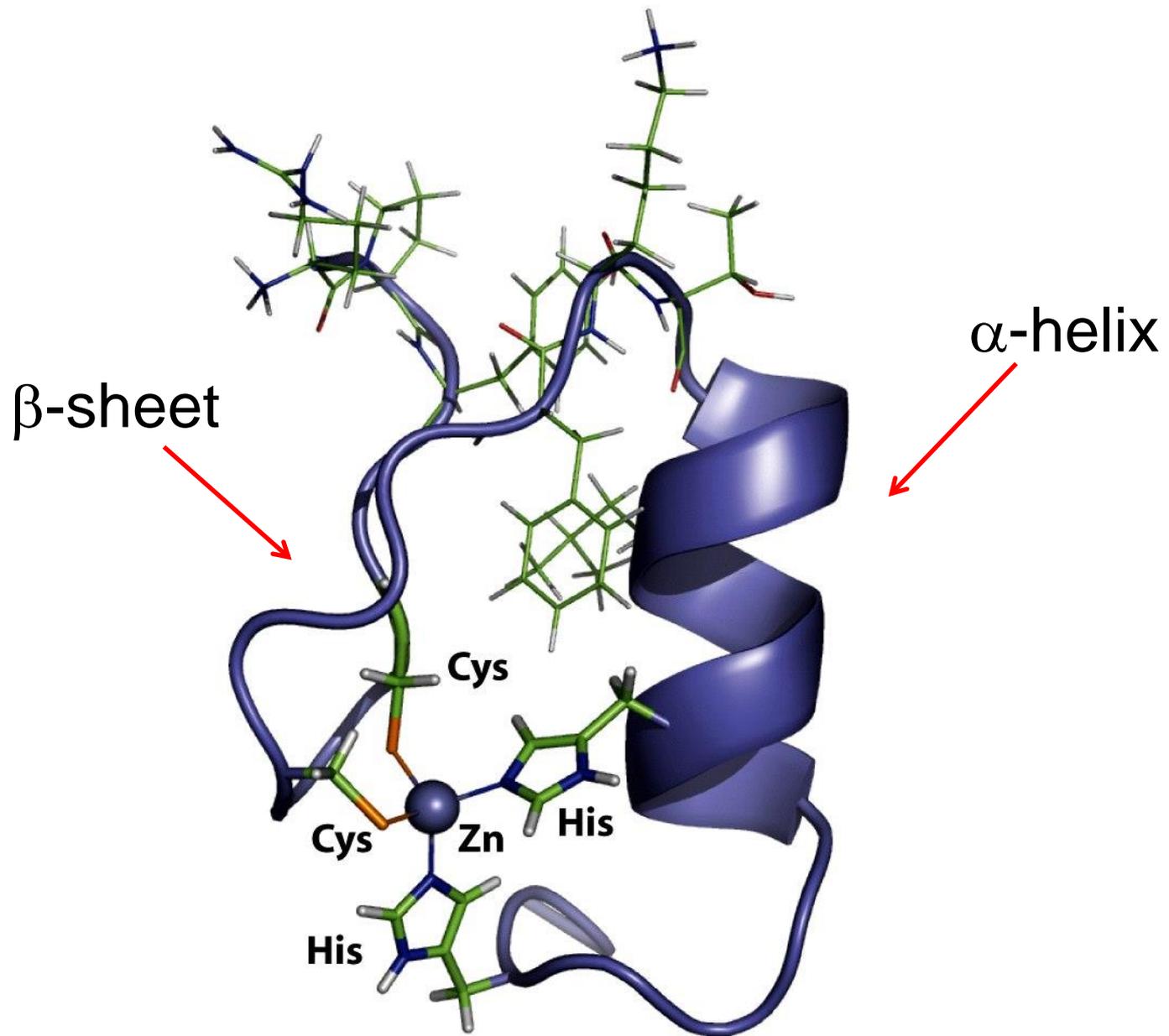
# Active site of HDAC8 (histone-deacetylase 8)

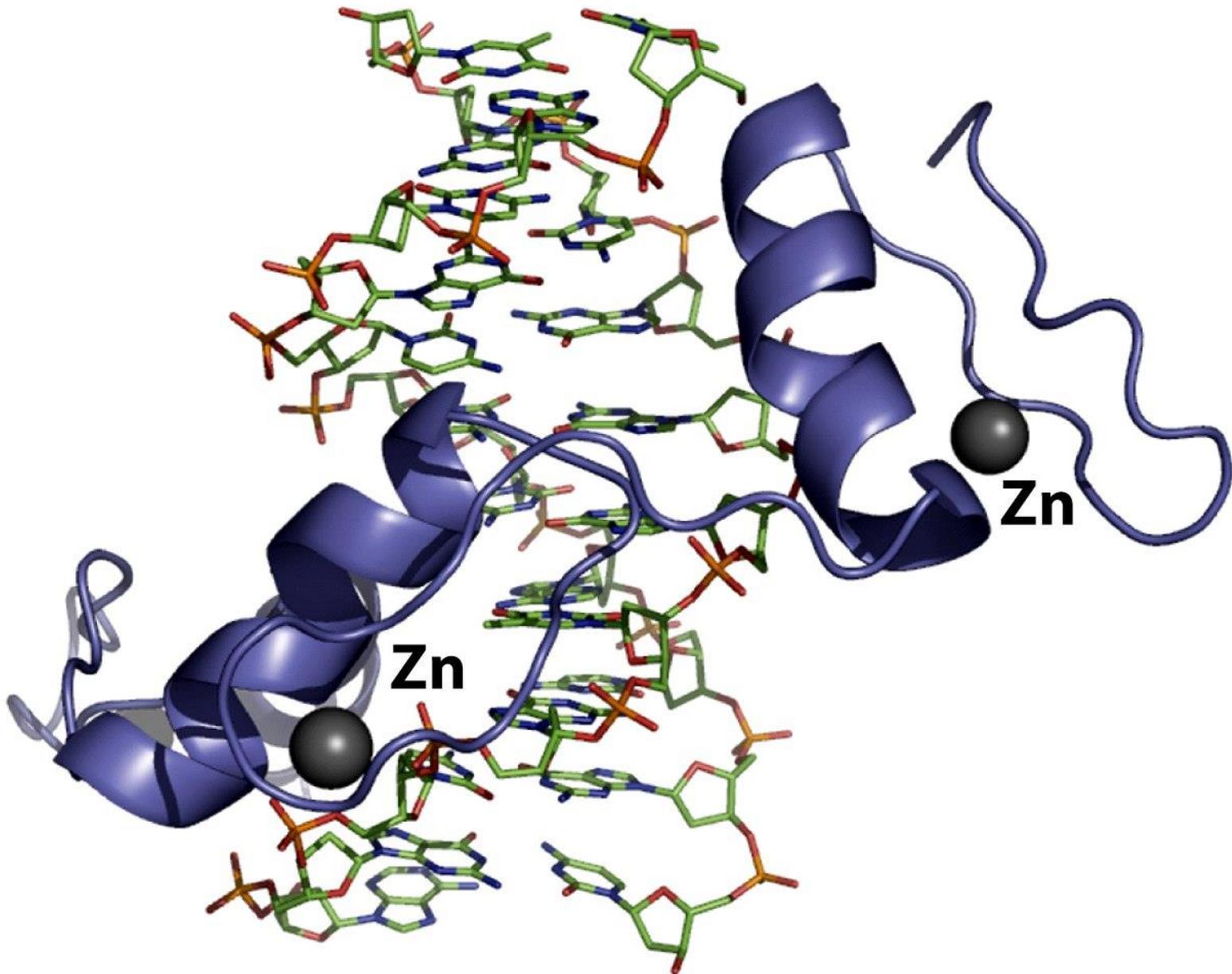


# Zinc fingers



*gene regulatory proteins e transcription factors*





Interaction between zinc-fingers and DNA