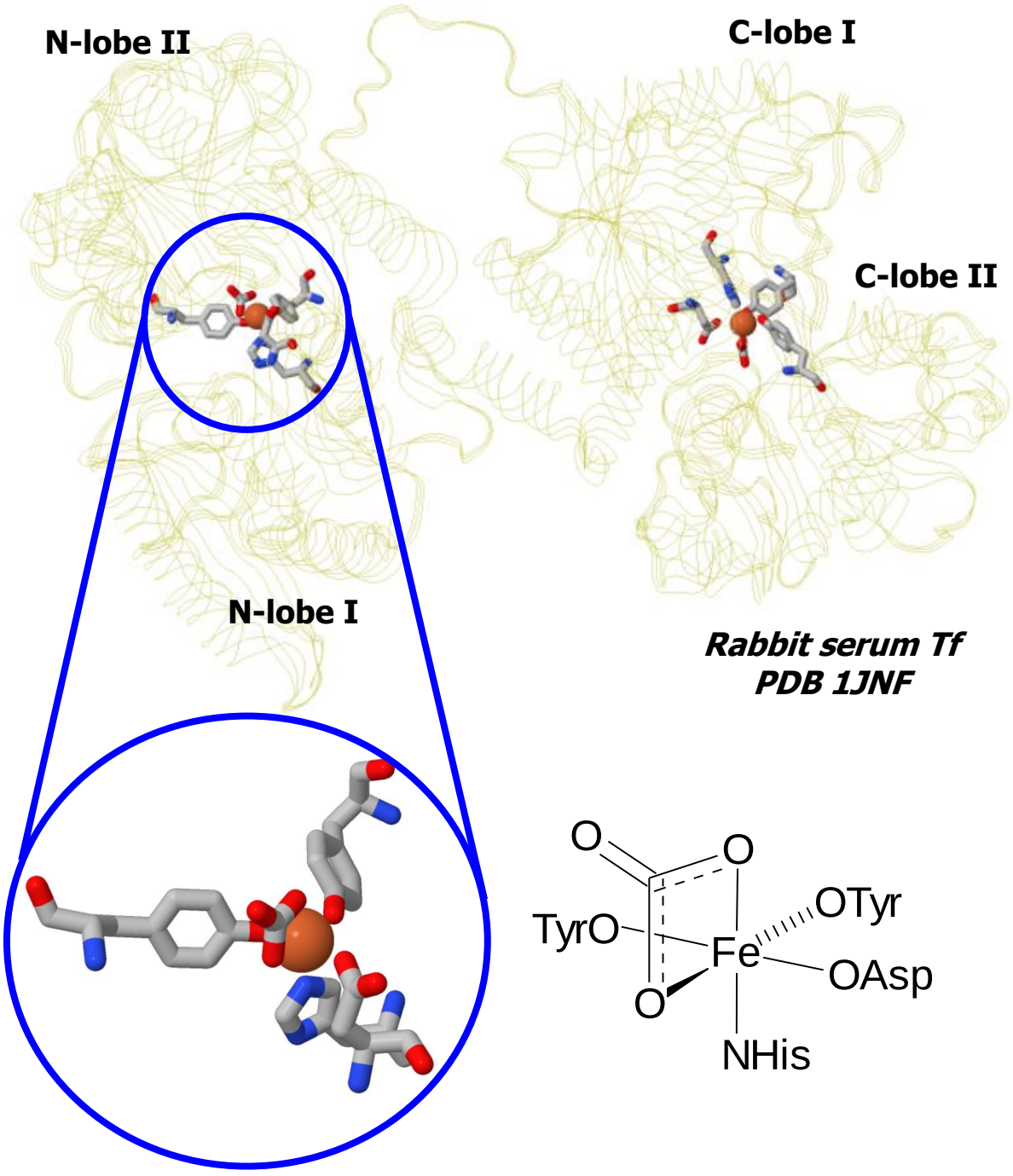
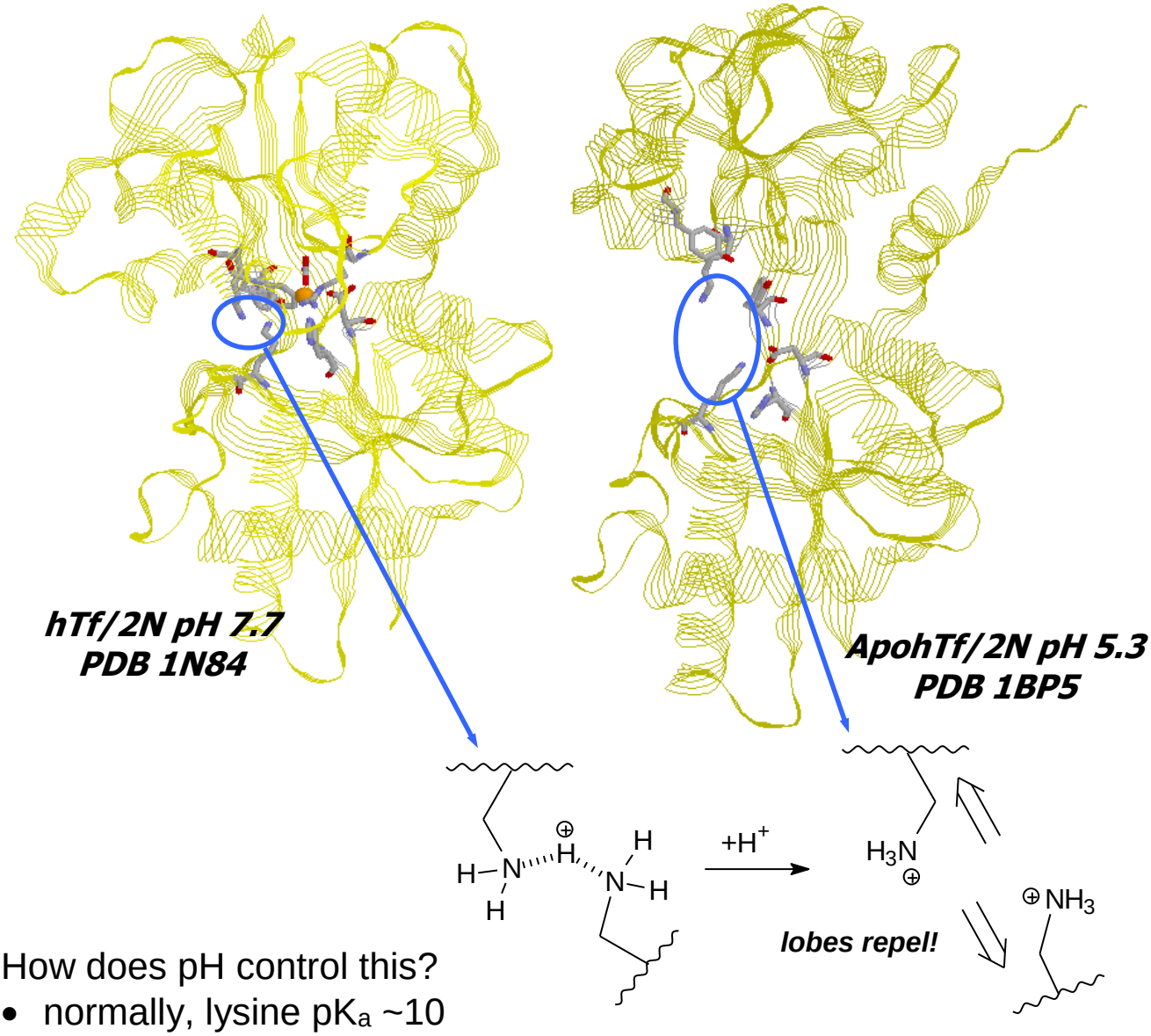
Transferrin

- used for Fe transport in vertebrates (some arthropods, molluscs)
- different types found in different fluids:
  serum Tf (blood), ovoTf (egg whites), lactoferrin (milk, saliva)
- ~80kDa, one chain, two lobes, each lobe has two domains
- each lobe binds one Fe(III),
  octahedral 2×OTyr NHis OAsp + exogenous bidentate $[CO_3]^{2-}$



Only serum Tfs bind Fe reversibly under physiological conditions, used to deliver Fe to rapidly-growing cells

- serum Tf binds to cell receptor, endocytosed
- within cell, pH drops, triggering loss of Fe at pH ~5.5
- Fe uptake/release involves structural change:

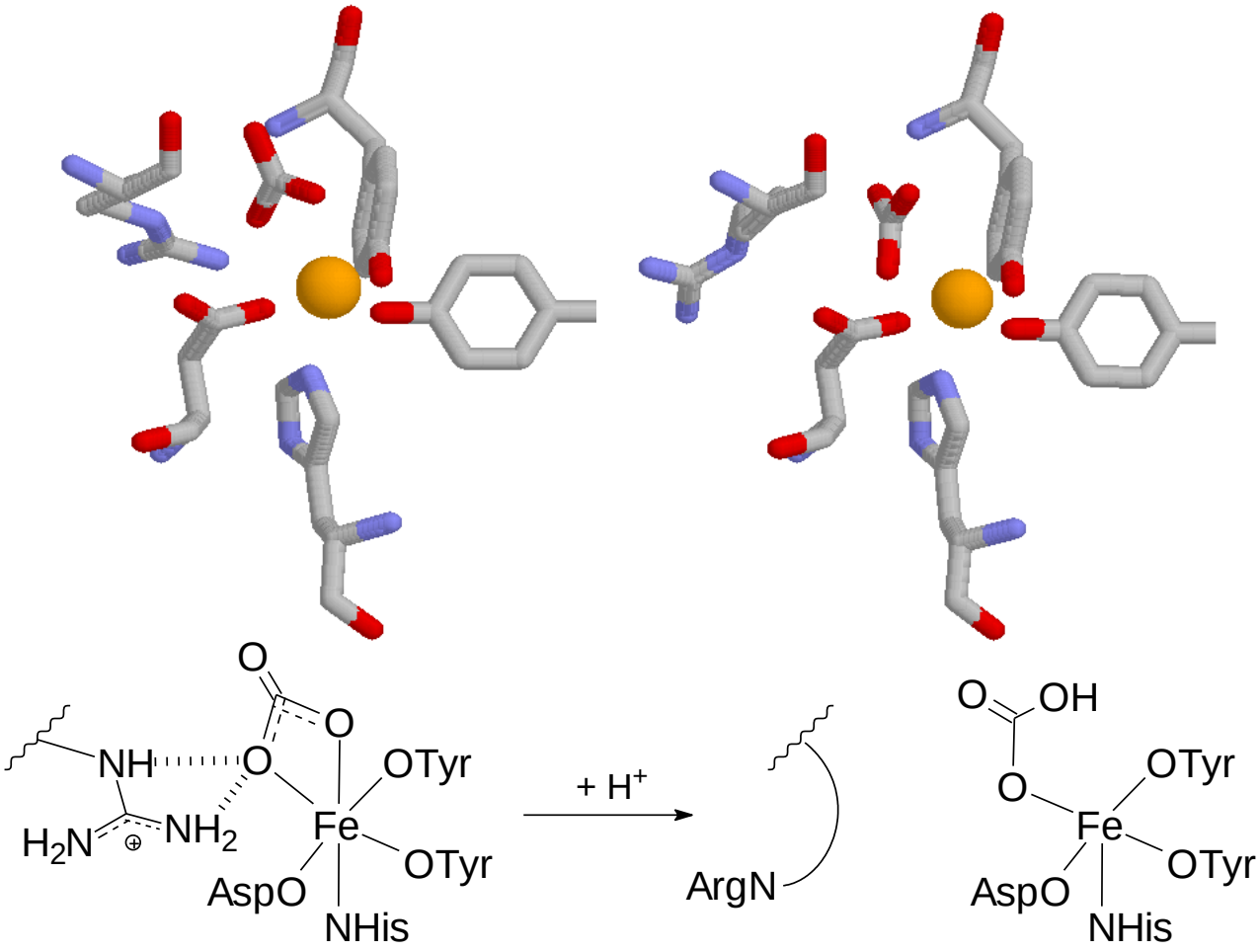


How does pH control this?

- normally, lysine pK_a ~10
- dilysine bridge pK_a ~7
- protonate bridge, two (+) charges repel the lobes
  - mutation of either Lys residue retards Fe loss by ~100x

Protonation also weakens Fe binding

- $[CO_3]^{2-}$ held in place/shielded by H-bonds to Arg124
- with H^+, Arg124 swings out and $[HCO_3]^-$ shifts away
- loss of $[HCO_3]^-$ and protonation of His249 accompanies loss of iron



Although oTf and Lf have similar topology and identical Fe binding sites to serum Tf, they *do not reversibly release Fe*. Instead, they sequester it as a defence against bacteria. Key differences:

- retain Fe to pH ~3.5 or lower
- no dilysine bridge
- Lf has Arg124 “out” position sterically blocked
- oTf has Arg124 “in” position locked with salt bridge to Glu66