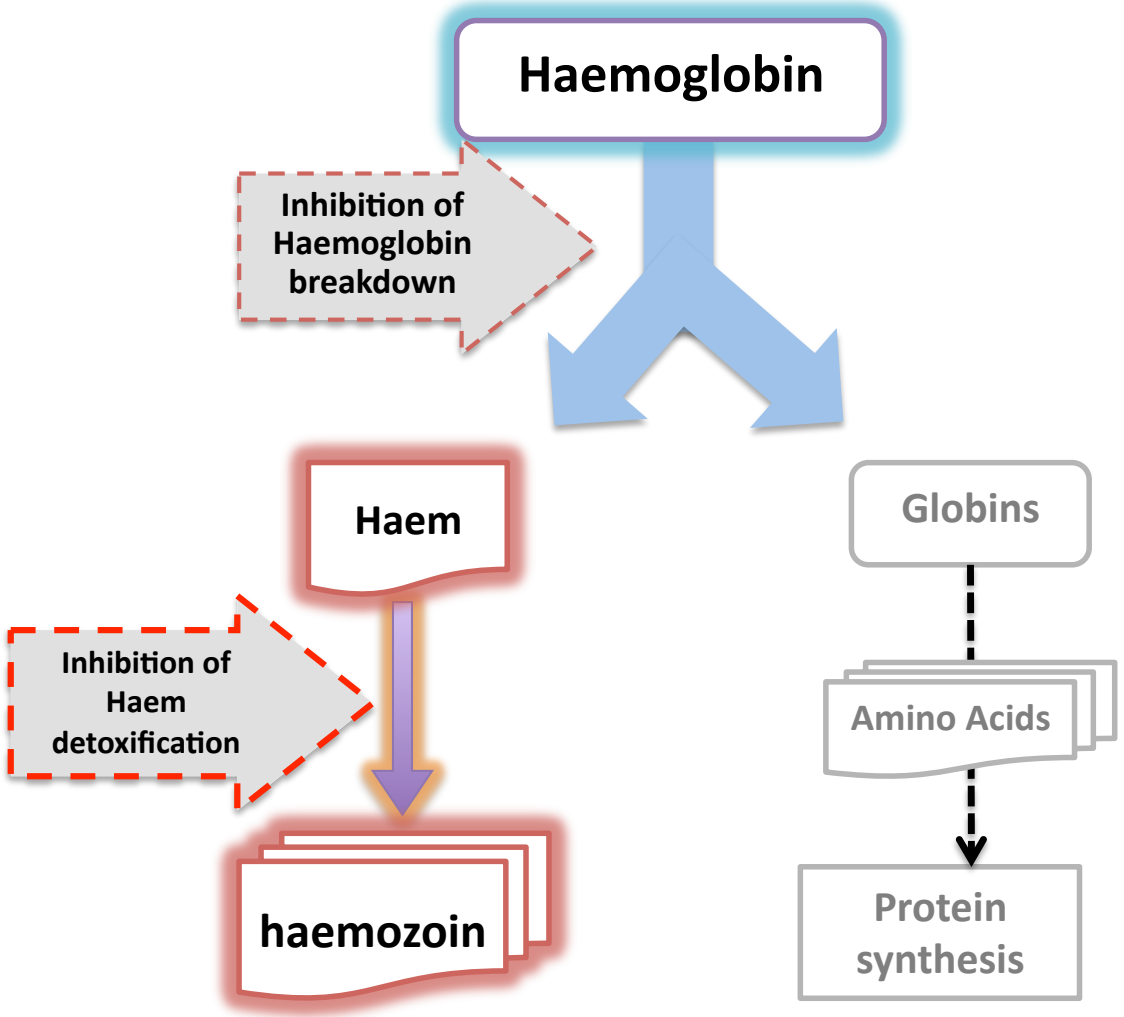
Haem Detoxification Protein

- a promising antimalarial drug target-

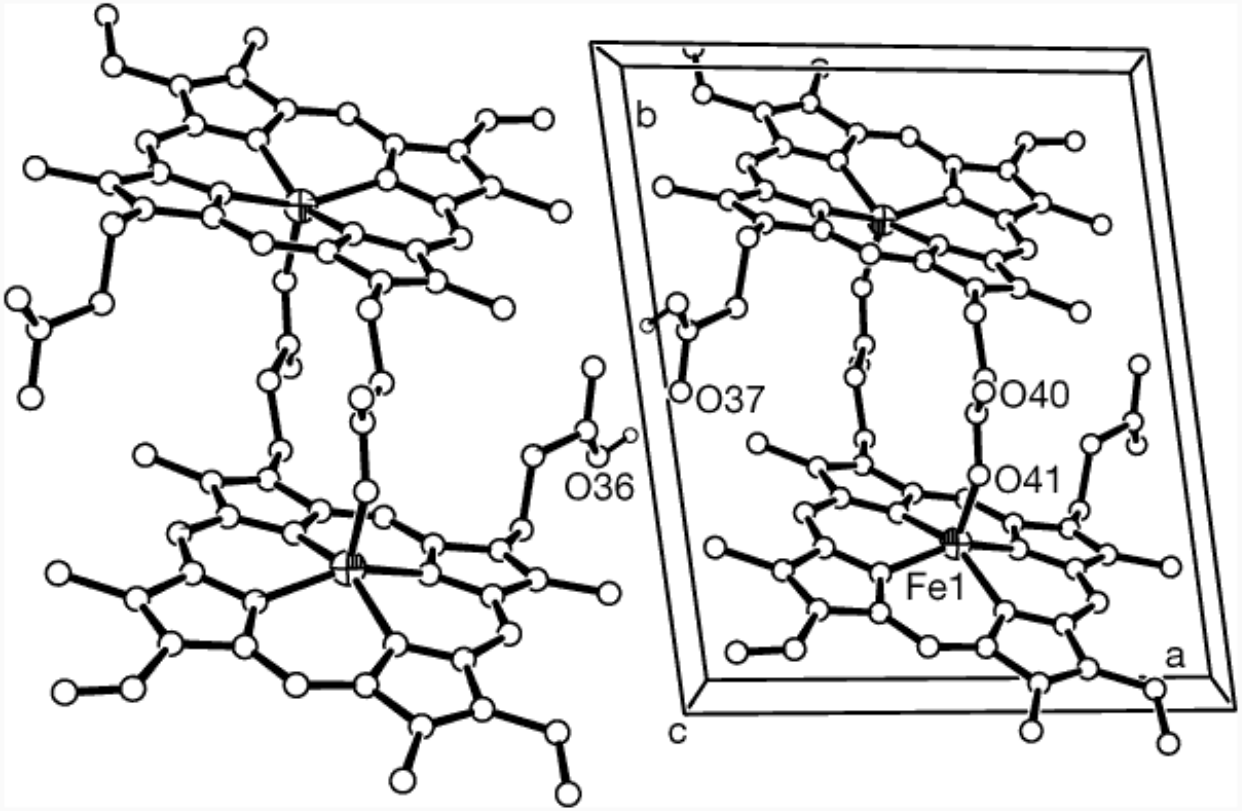
GITHAE, DEDAN K.

Supervisor: Andrea Schafferhans
(Rostlab)

Haem detox pathway and drug targets



Haemozoin dimerisation (Nature 404)



Formation of dimers occurs through Fe1–O41 bonds, whereas dimers are linked by hydrogen bonds through O36 and O37. All other hydrogens are omitted for clarity.

"…Due to an incomplete understanding about parasite processes that lead to haemozoin formation, a drug that specifically targets parasite factors… has never been developed…"

Dewal Jani, et.al (2008)

.

HDP (Haem detoxification protein)

Experimentally, HDP:

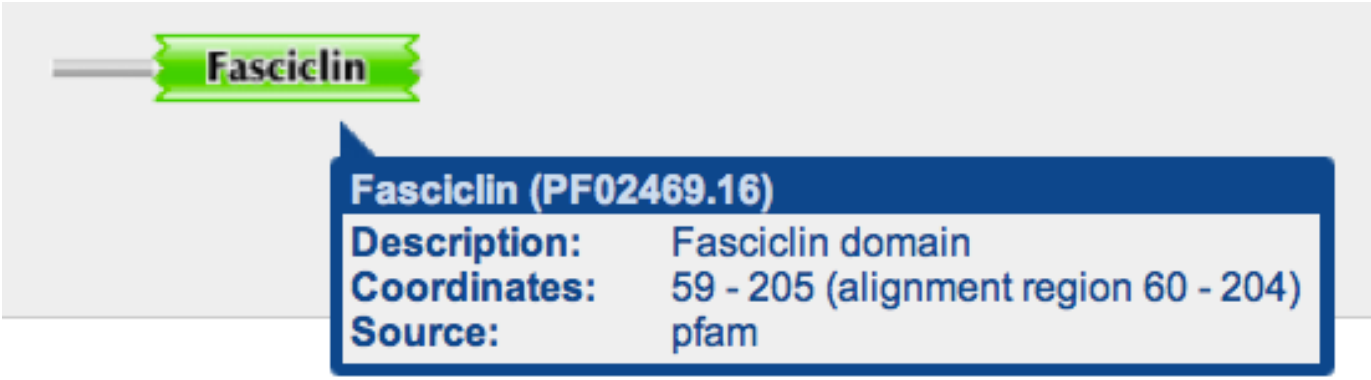
- Has high affinity for haem, with 2.7 Haem binding sites
- Is highly potent in haemozoin formation
- Optimal activity at low pH (4.5 – 5.2)
- No homology to haem binding proteins identified (..so far)

- Is conserved across the *plasmodium* species

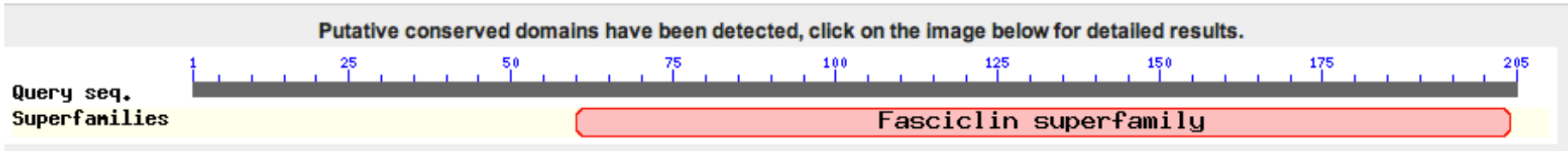
  * Heme detoxification in the human host is via different pathway (conversion to bilirubin)

- A **fasciclin** domain is identified for C-Terminal domain

Pfam



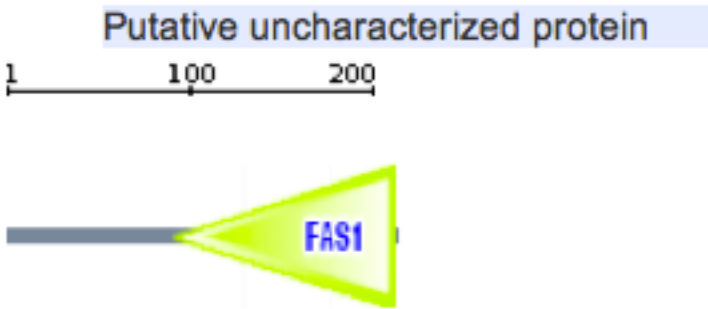
NCBI



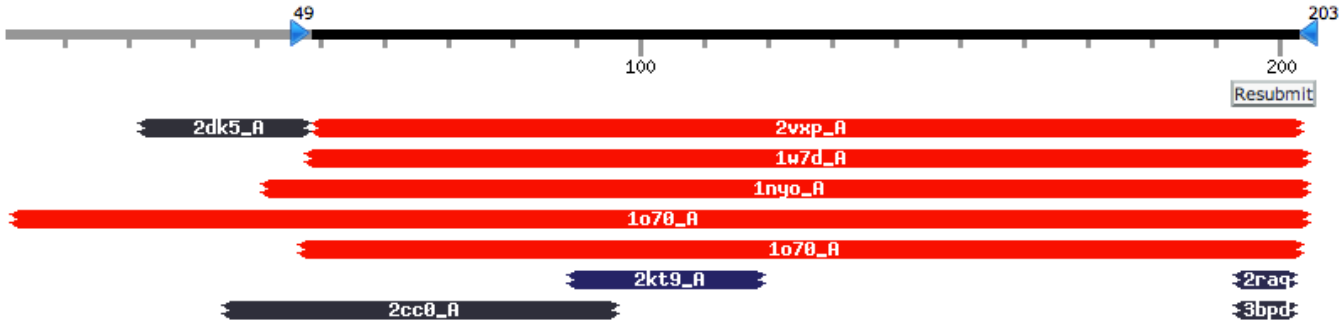
SMART

Position: 88 to 204

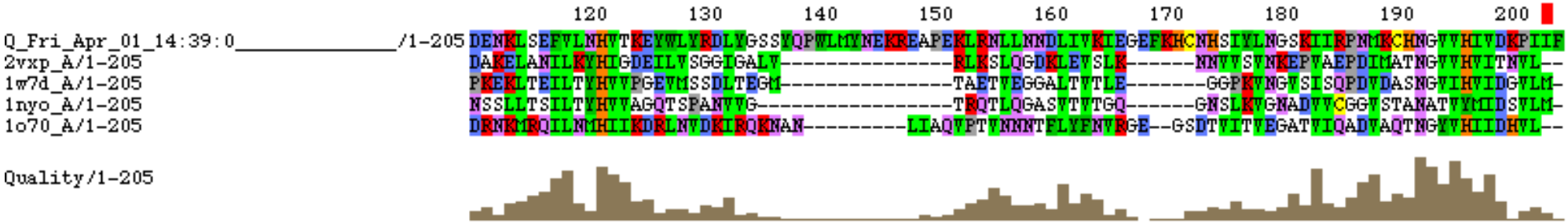
E-value:8.61e-09



Using profile search for templates (HHPRED)



Histidine conservation on templates



** Histidine residues are important for haem binding sites

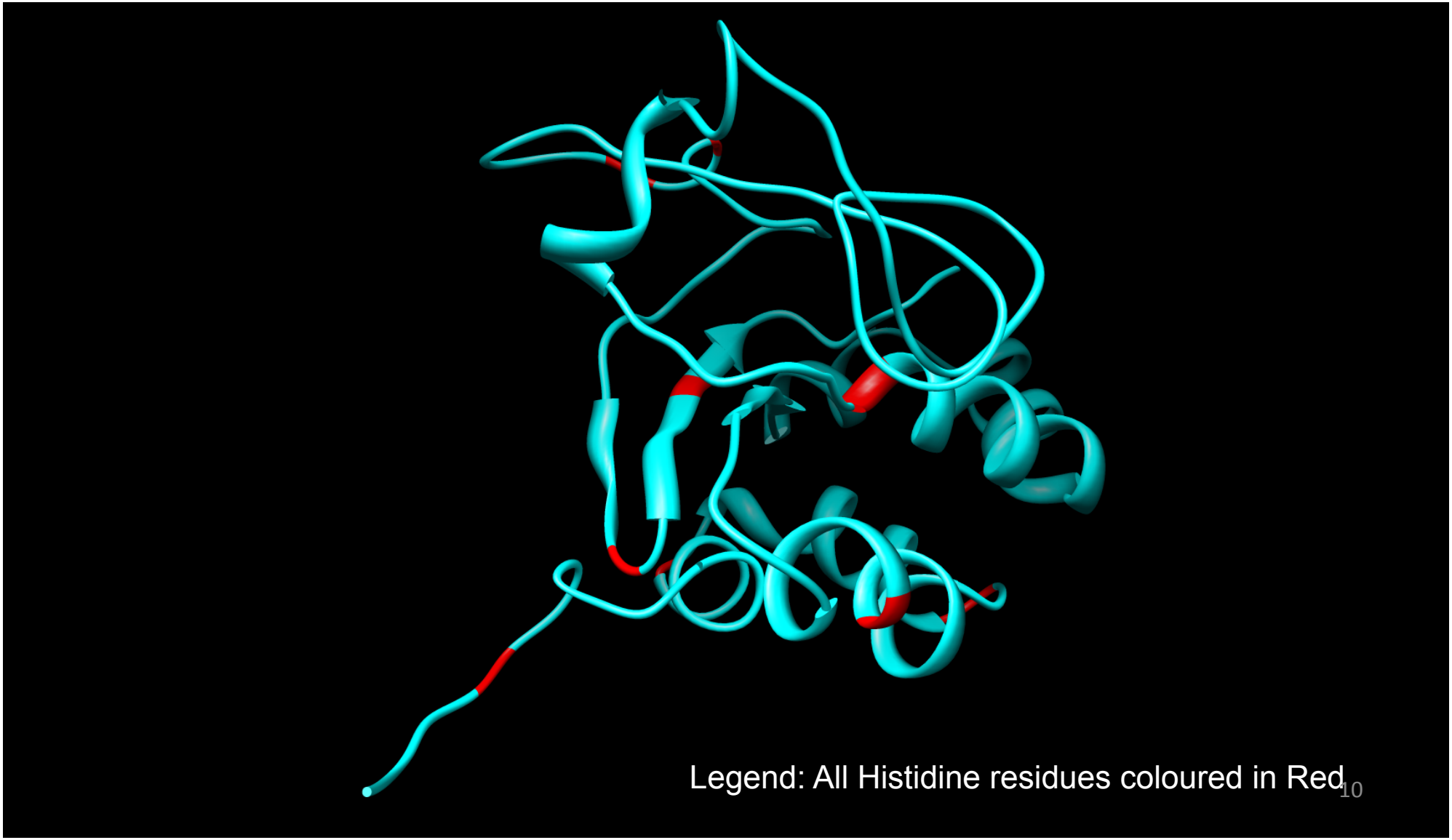
- HDP has 9 (out of 205) Histidine residues, which we propose are essential for haem binding.

HDP domain Modeling

- Modeller 9v8 was used to create models of HDP C-terminal domain covered by templates.

- No obvious arrangement of histidines to indicate haem binding site.

HDP model



Legend: All Histidine residues coloured in Red

Next steps…

- Looking at other haem binding sites
- Protein-protein docking of HDP monomers to find dimerisation interface
- Try dock dimerised to modelled HDP dimer
- Comparison of Model vs de novo model of HDP

Thank you!