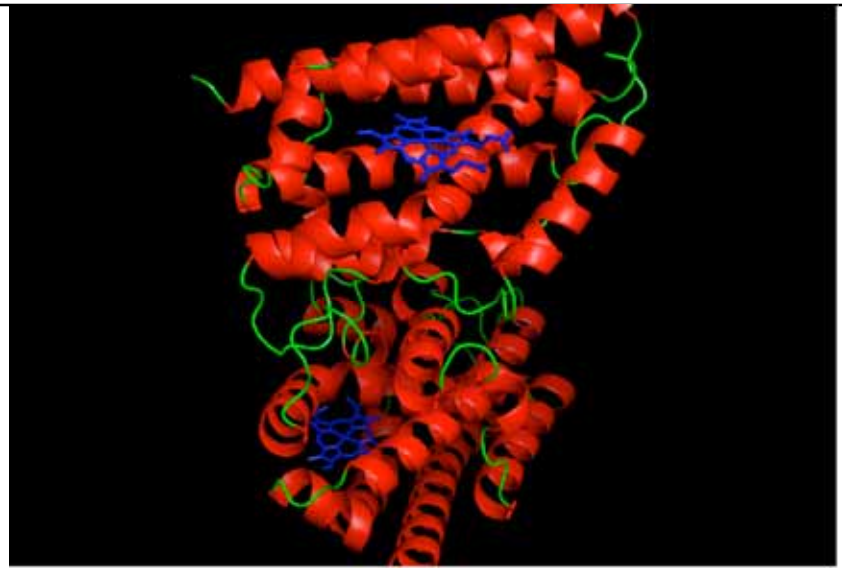
UMassAmherst

Human Heme Oxygenase-1



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HEME?

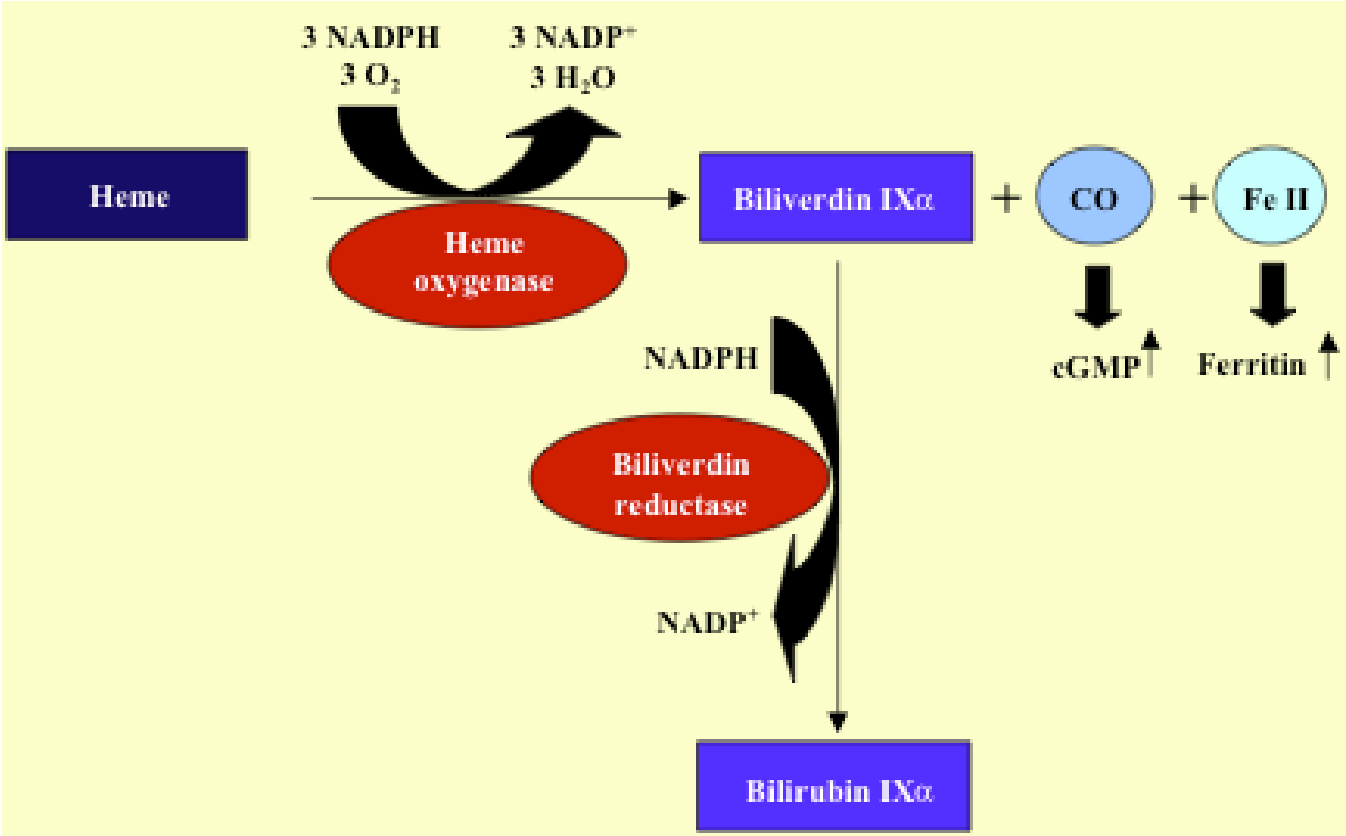
Heme released from oxidized free hemoglobin constitutes a potentially harmful molecule due to its ability to intercalate into cell membranes where it promotes deleterious iron-dependent reactions leading to ROS generation and membrane lipid peroxidation

Introduction

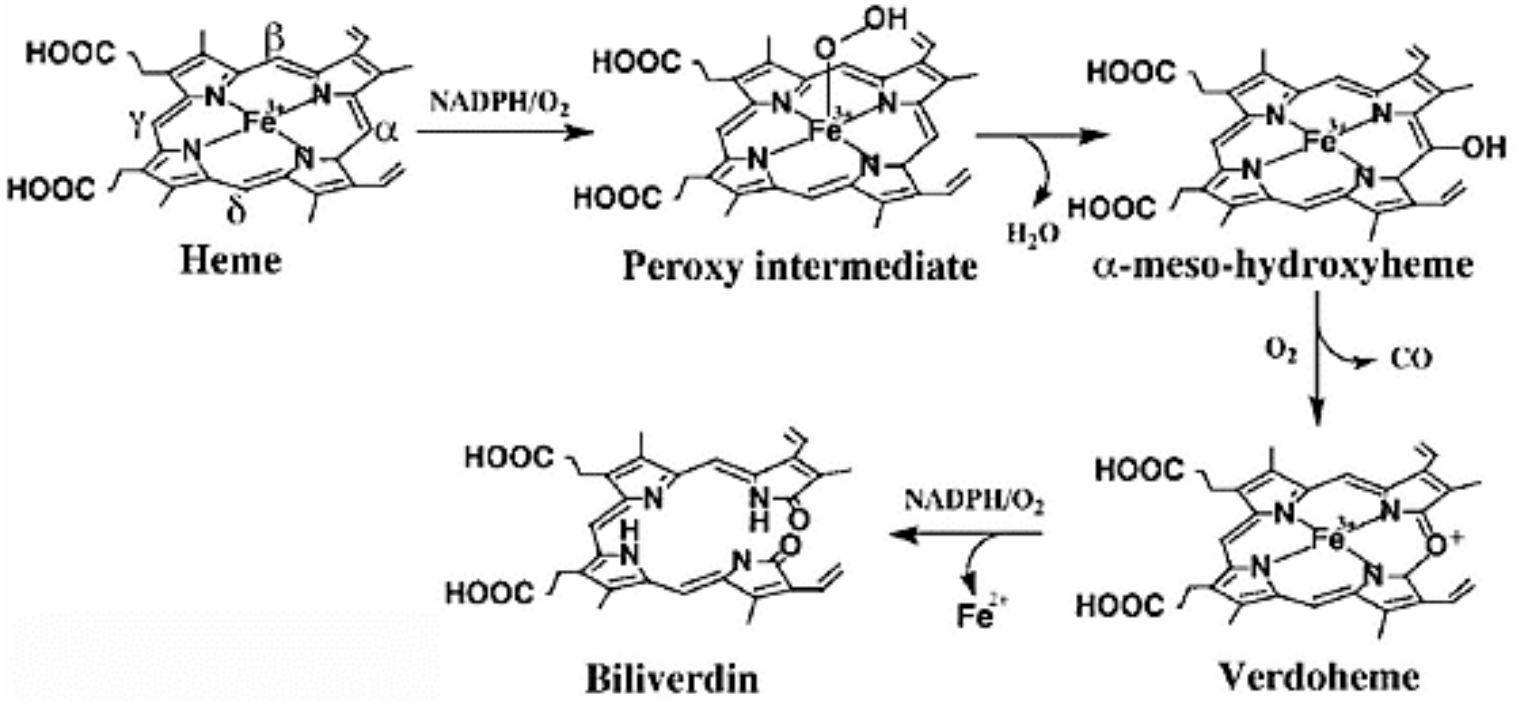
- Discovered in 1968 by

  Tenhunen R, Marver HS and Schmid R
- HO1 is expressed at low levels in endothelial cells, as well as in kidney, liver, and most abundantly in spleen, where senescent erythrocytes are sequestered and red blood cell hemoglobin is degraded
- Together with the heme synthetic enzyme δ-aminolevulinate synthase it regulates the cellular levels of the prooxidant heme, yielding equimolar amounts of biologically active catabolites
- HO-1 catalyzes the first and rate-limiting step in heme degradation.
- In the HO reaction, the oxidation of heme generates equimolar ferrous iron, biliverdin IX and CO.

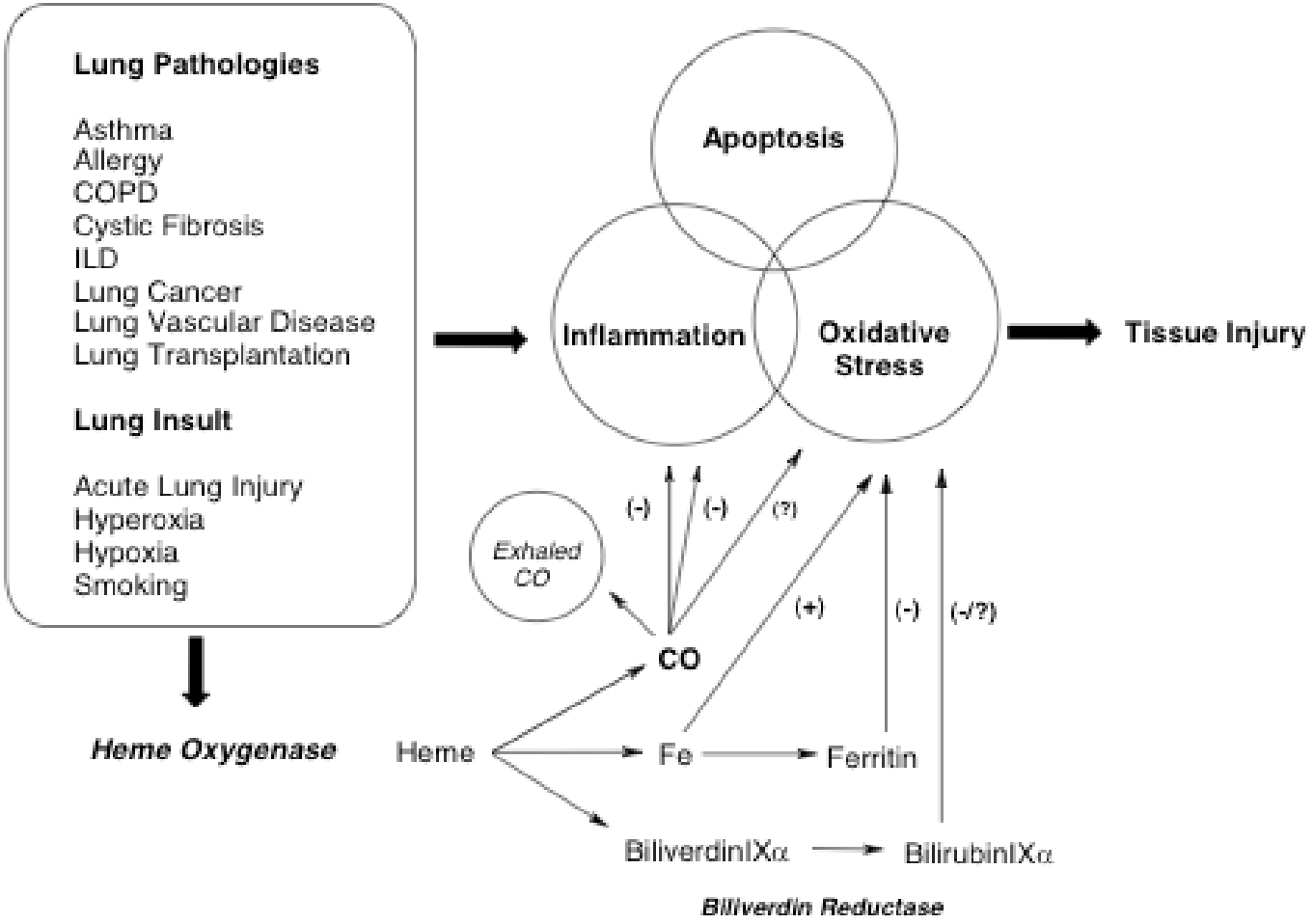
Mechanism


3 NADPH
3 O2
3 NADP+
3 H2O
Heme
Heme oxygenase
Biliverdin IXα
CO
Fe II
cGMP
Ferritin
NADPH
Biliverdin reductase
NADP+
Bilirubin IXα

Mechanism


HOOC
β
γ
α
δ
Fe
N
HOOC
Heme
NADPH/O2
OH
O
Peroxy intermediate
H2O
α-meso-hydroxyheme
OH
O2
CO
Verdoheme
NADPH/O2
Fe2+
Biliverdin

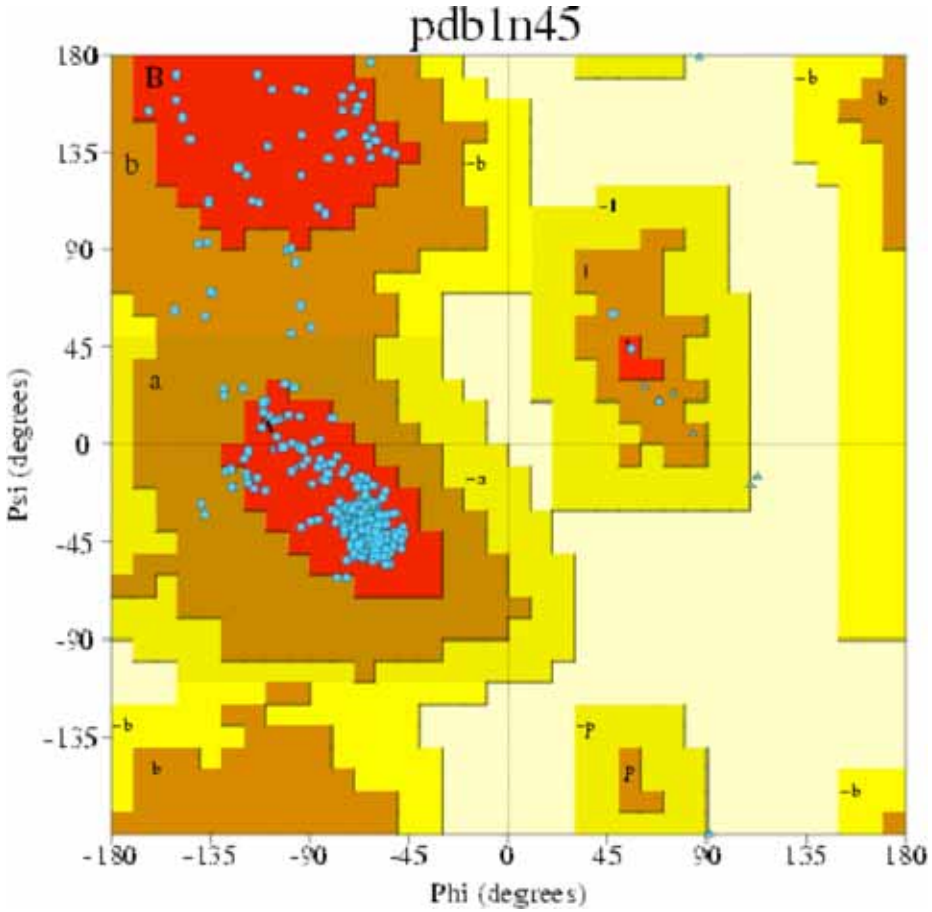
Role


Lung Pathologies
Asthma
Allergy
COPD
Cystic Fibrosis
ILD
Lung Cancer
Lung Vascular Disease
Lung Transplantation
Lung Insult
Acute Lung Injury
Hyperoxia
Hypoxia
Smoking
Heme Oxygenase
Apoptosis
Inflammation
Oxidative Stress
Tissue Injury
Exhaled CO
(-)
(-)
(?)
(+)
(-)
(-/?)
CO
Heme
Fe
Ferritin
BiliverdinIXα
BilirubinIXα
Biliverdin Reductase

Structure

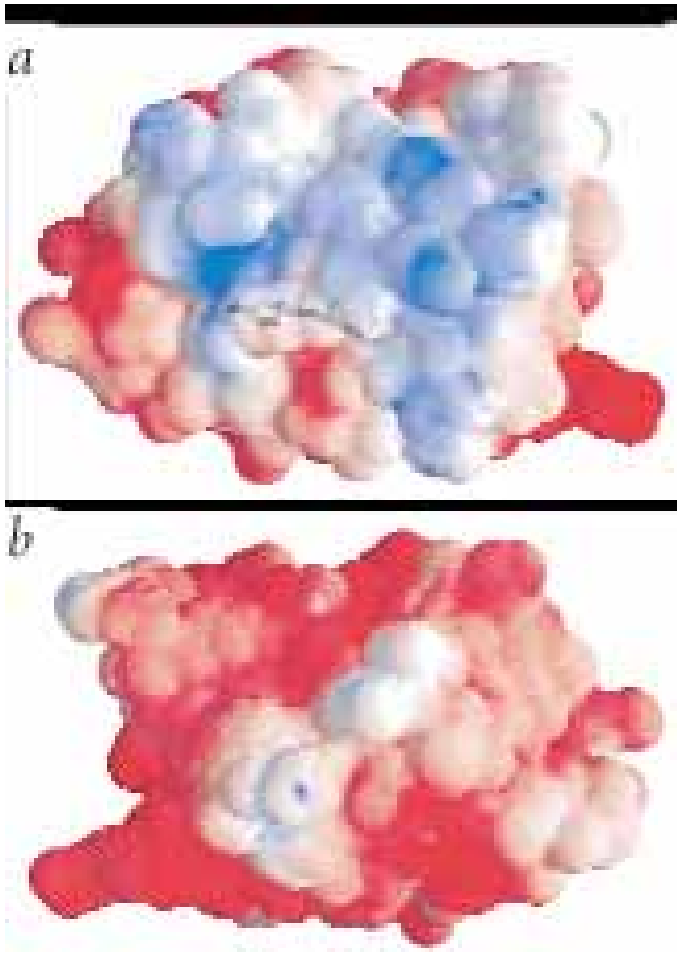
- 1N45
- Resolution: 1.50 A°
- 2 HO in asymmetric unit
- 233 residues per unit
- Mostly α-helical
- 12 helices
- The heme is sandwiched between two helices

Structure



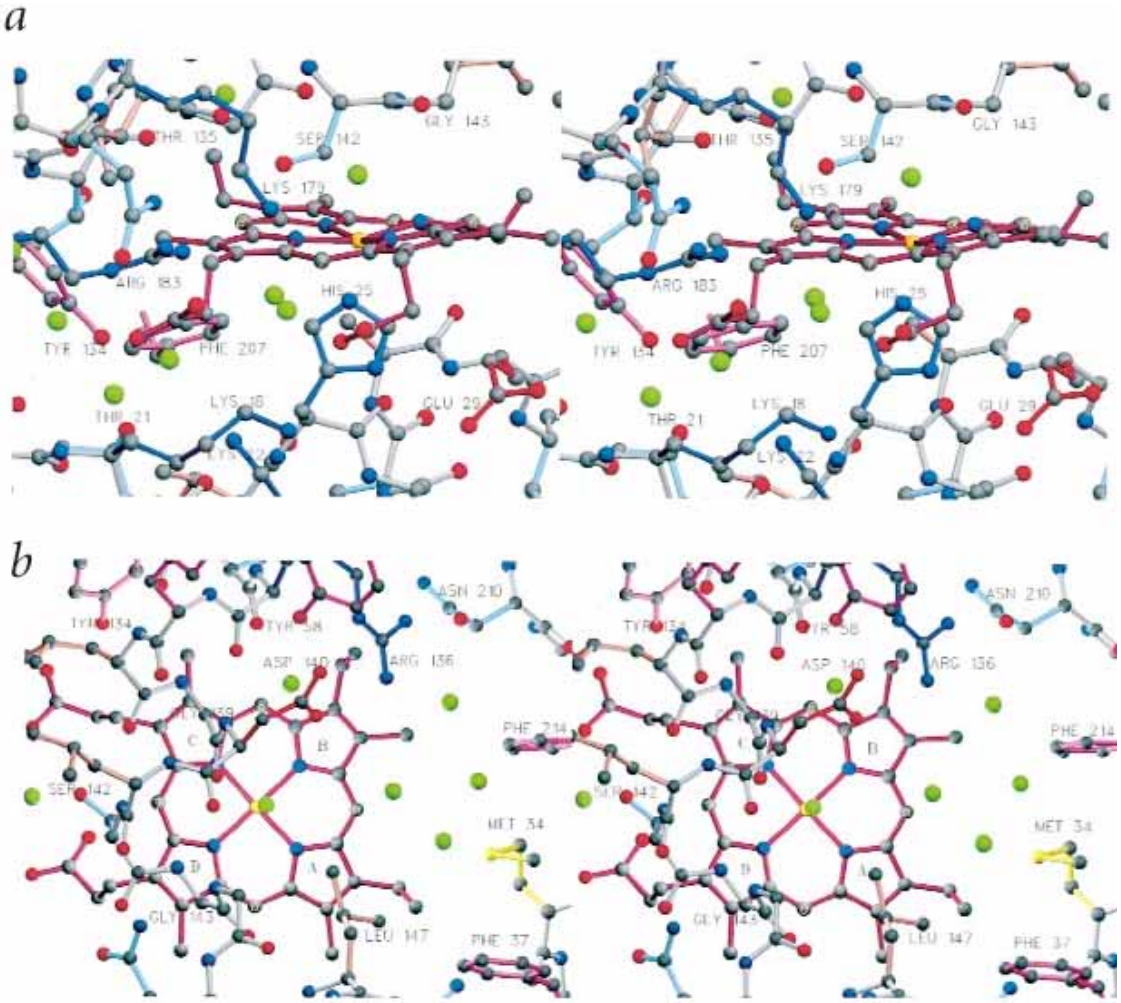
- Most favored regions: 93.8%
- Additional allowed regions: 6.2%

ES potential



- Potential on surface surrounding the exposed edge of heme is positive
- Electron donor is docking there
- (positive: blue)
  (negative: red)

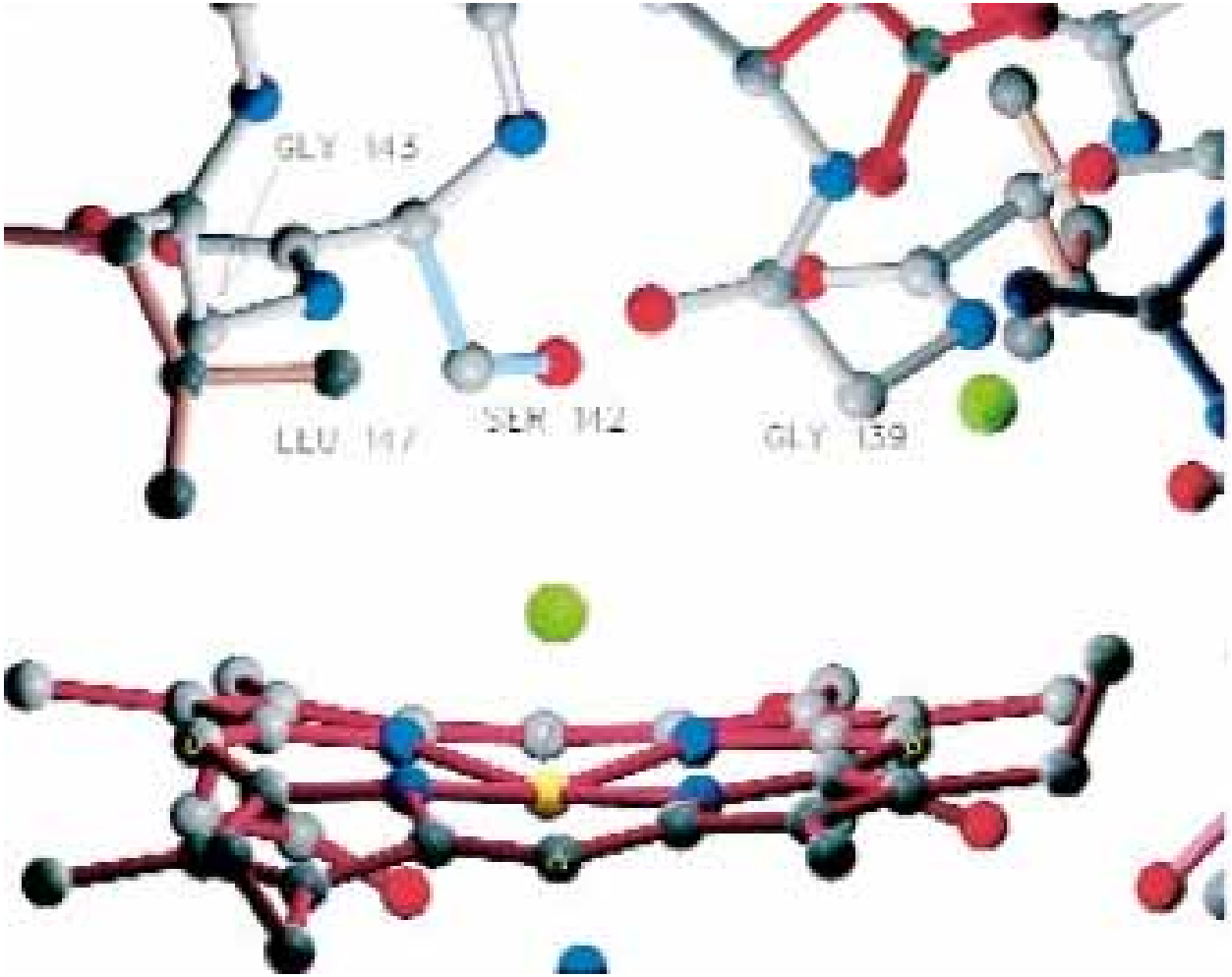
HEME contact



The active site of HO-1.
a, Stereo view of the heme site from the outside of the molecule, showing proximal residues

b,Stereo view of the distal side of the heme from above the distal helix.

Distal helix



References

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- Latesh Lad, David J. Schuller, Hideaki Shimizu, Jonathan Friedman, Huiying Li, Paul R. Ortiz de Montellano, and Thomas L. Poulos. Comparison of the Heme-free and -bound Crystal Structures of Human Heme Oxygenase-1. J. Biol. Chem. 278: 7834-7843.
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