Oxygen Carriers

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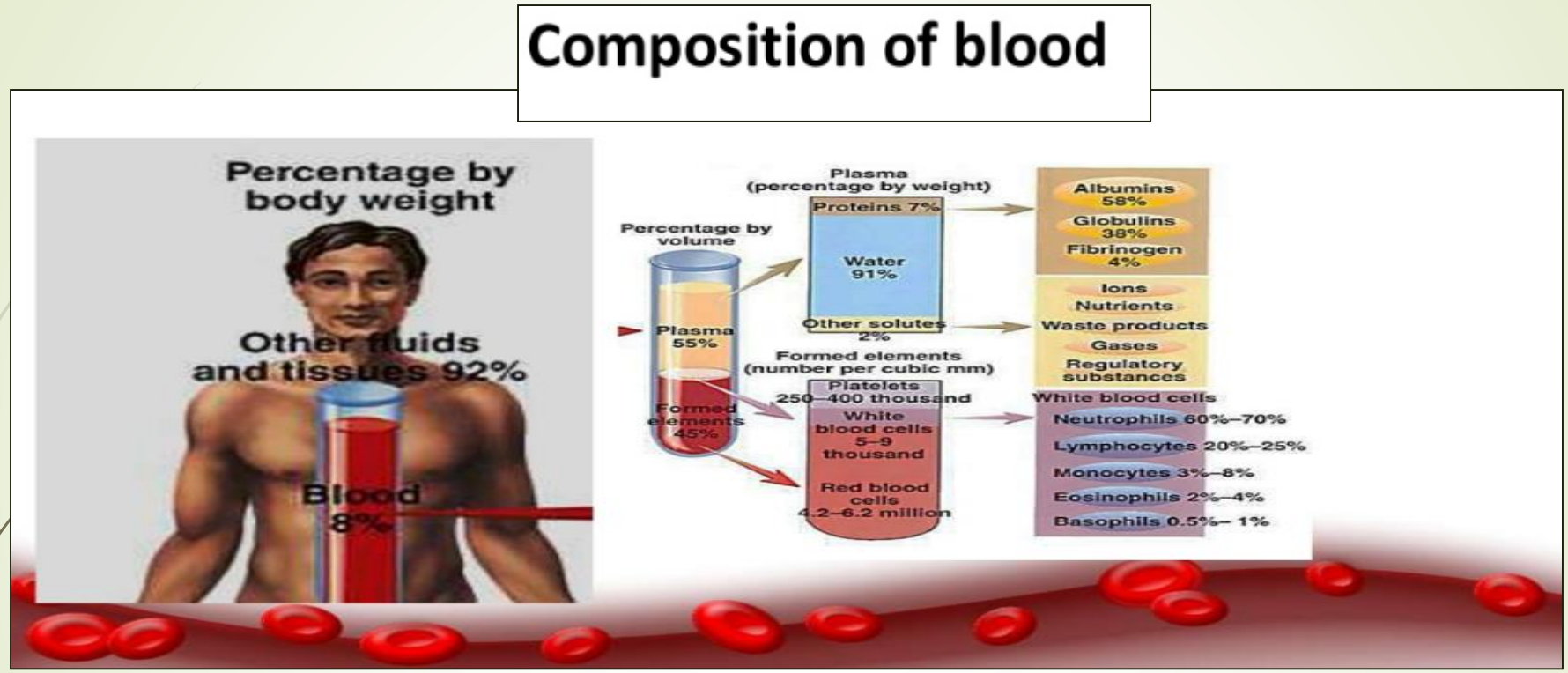
Introduction



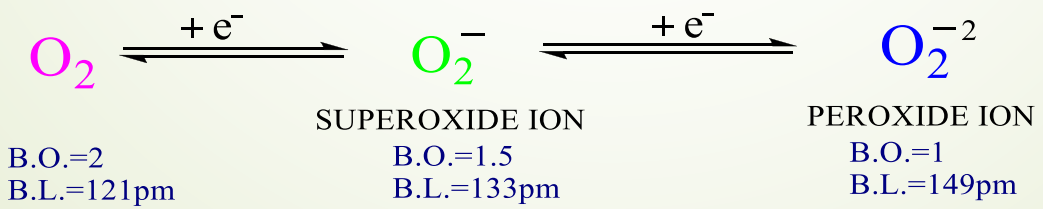
- *The main function of red blood cell is -*
  Transfer of O_2 from lungs to tissue.
  Transfer of CO_2 from tissue to lungs.
- *To accomplish this function red cells has Oxygen carriers.*

- All aerobic forms of life depends on **Oxygen Carriers**.
- The transport and storage of Oxygen is extremely important physiological function and this is done by oxygen carriers.
- Various types of oxygen carriers occurring in living systems are -

Oxygen carriers	**Found in**	**Metal Present**	**Function**
Hemoglobin (Hb)	All Mammals	Fe(II)	Carrier
Hemerythrin (Hr)	Various marine invertebrates	Fe(III)	Carrier
Myoglobin (Mb)	All Mammals	Fe(II)	Storage
Hemocyanin (Hc)	Arthropods & Molluscs	Cu(II)	Carrier

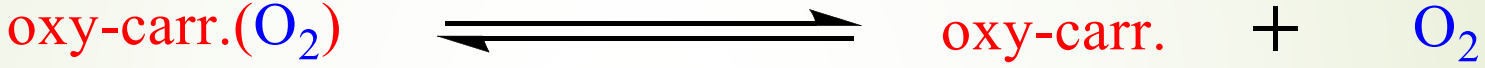
Dioxygen as Ligand

- *Under appropriate circumstances, Dioxygen molecule become a ligand and this process is called **OXYGENATION** in which oxygen molecule retains its identity.*
- *In ground state of oxygen molecule, **it has two unpaired electrons in $\pi^*(2p_y)^1$ and $\pi^*(2p_x)^1$ antibonding molecular orbitals.***
- *The degeneracy of π-molecular orbital leads to Biradical Character of oxygen molecule.*
- *The binding of dioxygen by a transition metal involves electron transfer reaction from metal to dioxygen forming a coordinated superoxide ion.*
- *The coordinated superoxide ion binds to the metal in an angular as opposed to a perpendicular fashion and usually has a partial negative charge concentrated on the terminal oxygen atom. This superoxide ligand may be stabilized by an electrophile in the distal cavity, for example, the formation of a hydrogen bond.*



What are the Oxygen Carriers??

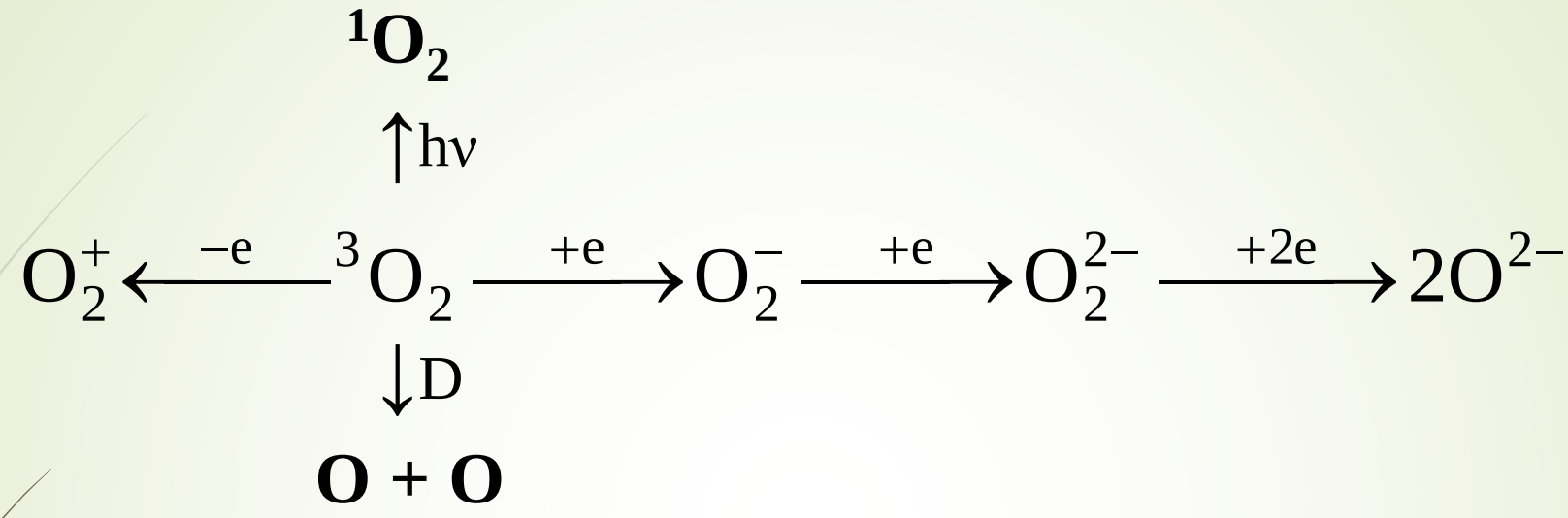
- **Oxygen carriers are compounds which can take up and release the oxygen *reversibly*.**



- **Oxygen carriers are needed in biological system as solubility of Oxygen is very low in water and it is 30 times more in Blood than water. Therefore oxygen has to be circulated inside body via blood.**

- **In the absence of oxygen carrier, the amount of oxygen will be very low and person will suffers from HYPOXIA.**

Activation and reactions of the oxygen molecule



1. Generated states:

Ground state: $^3O_2$ **(triplet:** $\pi^* \uparrow\uparrow$ **)**

Generated state: $^1O_2$ **(singlet:** $\pi^* \uparrow\downarrow$ **)**

The generated state is usually formed through a „mediator molecule" (photosensibilisator, S):

$$^3O_2 + {}^1S \xrightarrow{h\nu} {}^1O_2 + {}^3S$$

Activation and reactions of the oxygen molecule

2. Ionisation of the oxygen molecule:

$$O_2 \xrightarrow{-e} O_2^+$$

$I_{O2} \sim I_{Xe}$ *ionisation energy*

It occurs only with extremely strong oxidizing agents (e.g. PtF_6)

3. Dissociation of the oxygen molecule:

$$O_2 \rightarrow O + O \quad (+ D_{O2})$$

The energy requirement (D_{O2}) of dissociation is relatively large:
→ burning takes place fairly readily at high temperature

Interactions of the Oxygen molecule with metal complexes

$$ML_n + O_2 \overset{K}{\longleftrightarrow} ML_nO_2$$

$$ML_nO_2 \xrightarrow{k} ML_{n-1} + L_{ox.} + H_2O_2 \ \ (\text{or } H_2O)$$

Two extreme possibilities:

1. **“ K” is high and “k” is low: oxygen carrier complexes**
   (e.g. hemoglobin, myoglobin, hemocyanin, etc.)

2. **“K” is low, but “k” is high: redox catalysis**
   (e.g. oxygenases, oxidases, etc.)

Reactions of the oxygen molecule in biology

1. Reversible binding of the oxygen molecule:

$$ML_n + O_2 \overset{K}{\longleftrightarrow} ML_nO_2$$

Binding of oxygen in different forms:

- $M^{n+} + O_2 \leftrightarrow M^{n+}O_2$ *(molecular form)*
- $M^{n+} + O_2 \leftrightarrow M^{n+1}(O_2^{-})$ *(superoxide radical)*
- $M^{n+} + O_2 \leftrightarrow M^{n+2}(O_2^{2-})$ *(peroxide, monomer)*
- $M^{n+} + O_2 \leftrightarrow (M^{n+1})_2(O_2^{2-})$ *(peroxide, dimer)*

2. Oxidases (dehydrogenases)

(Oxygen is reduced to peroxide or to water, it does not built in the substrate)

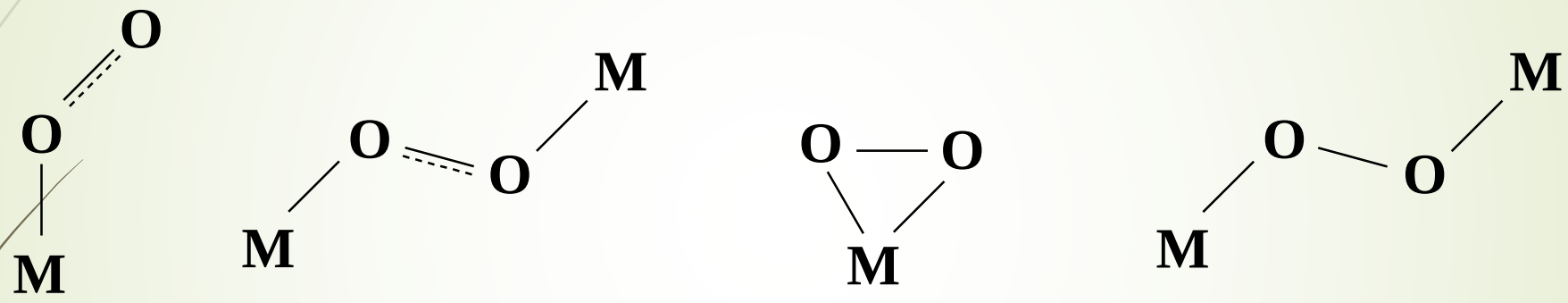
$$S + 2H^+ + O_2 \rightarrow S_{ox} + H_2O_2$$

$$S + 4H^+ + O_2 \rightarrow S_{ox} + 2\,H_2O$$

(e.g. cytochrome c oxidase, blue copper oxidases, etc.)

The posssible binding modes of O_2

as superoxo ligand **as peroxo ligand**



Bended (end-on) **bridging** **side-on** **bridging**

Reactions of oxygen molecule in biology

3. Oxygenases: ***(1 or 2 O atoms build in the substrate)***

- monooxygenases:

$$SH + O_2 + 2H+ \rightarrow SOH + H_2O$$

(e.g. cytochrome P_{450}, tyrosinase, etc.)

- dioxygenases:

$$SH + O_2 \rightarrow SO_2H$$

(e.g. tyrosinase, triptophane deoxygenase, etc.)

Reactions of oxygen molecule in biology

4. Decomposition of H_2O_2 (or peroxides):

- through reduction: peroxidases

$H_2O_2 + SH_2 \rightarrow S + 2\ H_2O$

- through disproportionation: catalases

$2\ H_2O_2 \rightarrow 2H_2O + O_2$

5. Decomposition of the superoxide radical anion:

superoxide dismutase – through disproportionation

$2\ O_2^- \rightarrow O_2 + O_2^{2-}$

e.g. CuZn-SOD, Fe(Mn)-SOD, ...

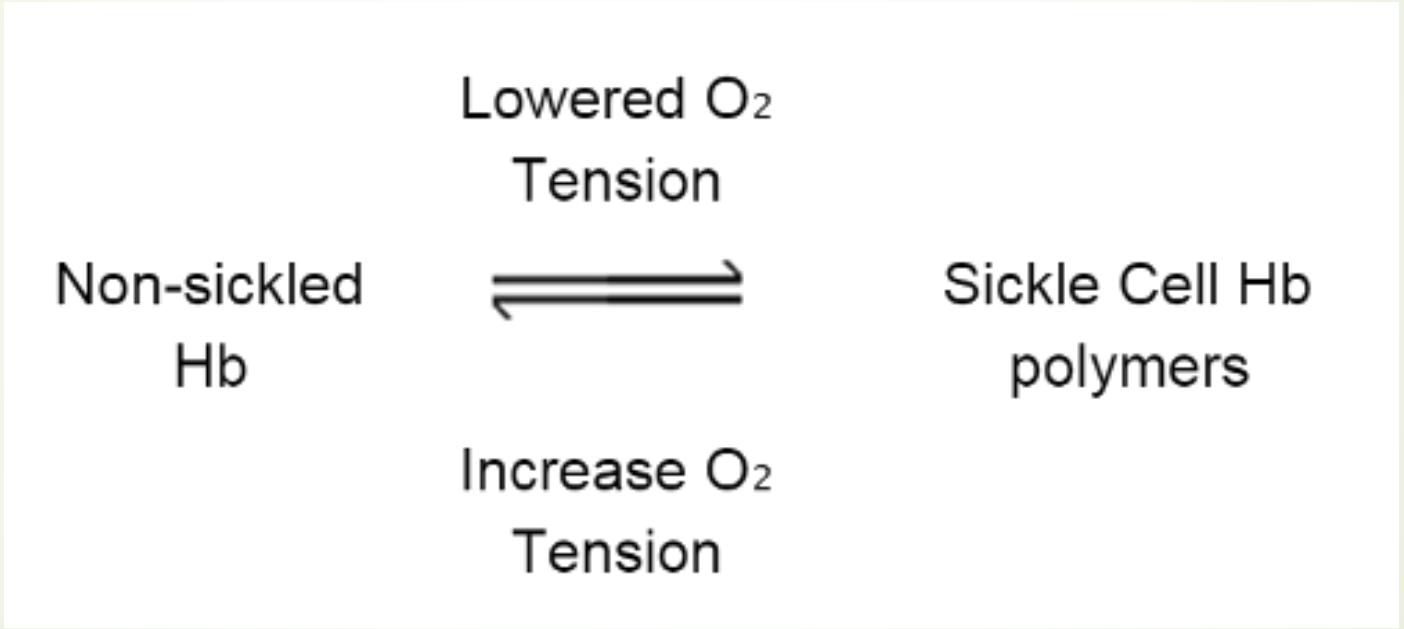
What causes red blood cells to sickle?

Sickle cell disease is an autosomal recessive disease commonly found in African populations. The disease gets its name from the fact that patients' red blood cells become sickle-shaped when passing through the capillaries of metabolically active tissues. These red blood cells become frail and can rupture long before their normal lifespan. The sickled red blood cells block capillaries and inhibit red blood cell function, causing severe anemia in sufferers.

The most common hemoglobin of adults is hemoglobin A (Hb^A). However patients suffering from sickle cell disease are homozygous for the allele coding for the abnormal variant of hemoglobin (Hb^S) due to a missense mutation in the gene encoding the β subunit of hemoglobin. This missense mutation replaces glutamic acid with valine at the sixth position of the β-globin chain.

The absence of a polar amino acid at this position promotes the non-covalent aggregation of hemoglobin in a low-oxygen environment which distorts red blood cells into a sickle shape and decreases their elasticity. Biochemically, the low oxygen environment causes the beta chain of neighbouring hemoglobin molecules to hook together, becoming rigid and polymerized. These cells fail to return to their normal shape when oxygen is restored and thus fail to deform as they pass through narrow vessels, leading to blockage in the capillaries.

In vitro studies of deoxygenation and reoxygenation of sickle-cell hemoglobin indicates that the process is reversible. The hemoglobin molecules polymerize and form crystals as oxygen concentration is lowered. But as the oxygen concentration is increased again, hemoglobin molecules can depolymerize and return to their soluble state. This can be written as:

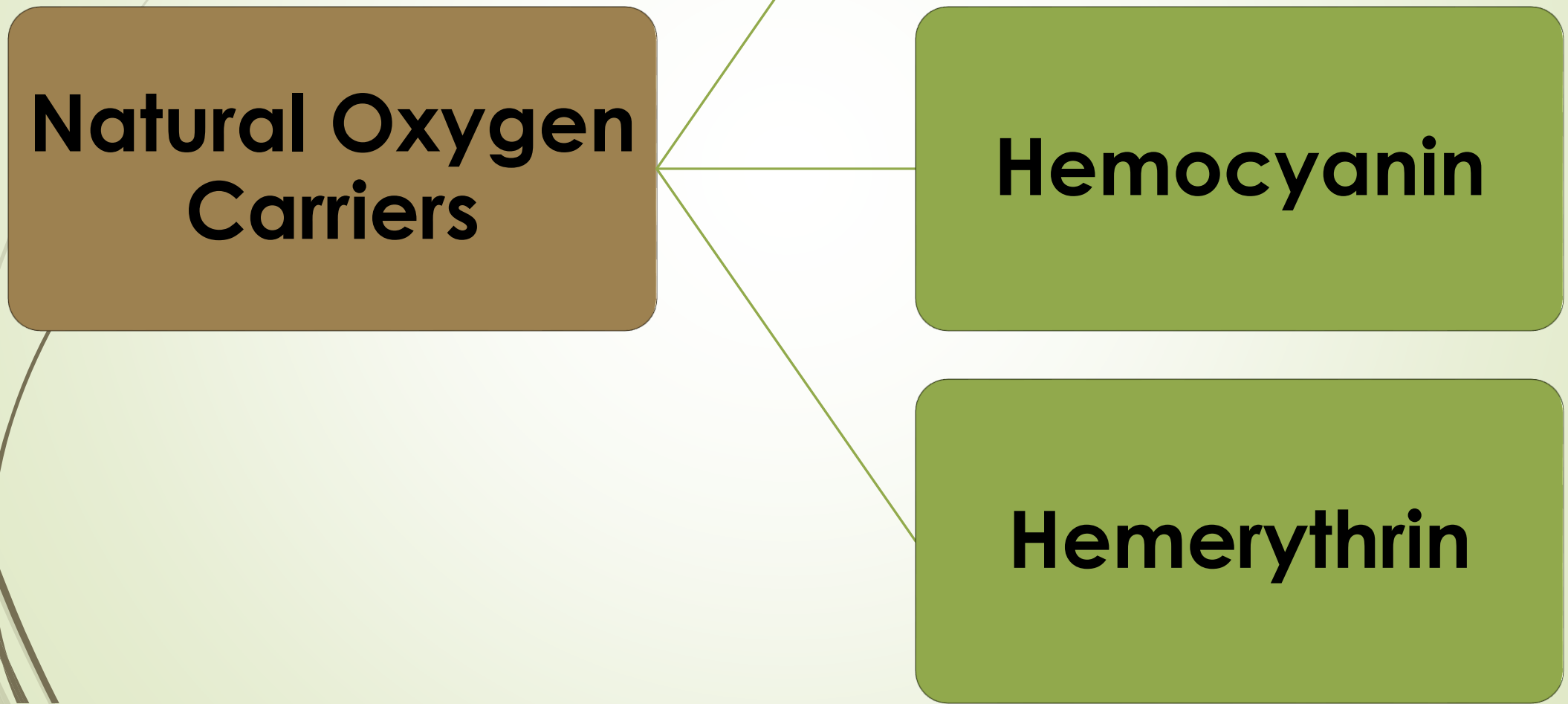


The equilibrium reaction equation relates non-sickled hemoglobin with sickle cell hemoglobin polymers

Types of Oxygen Carriers

Natural Oxygen Carriers

Synthetic or Artificial Oxygen Carriers

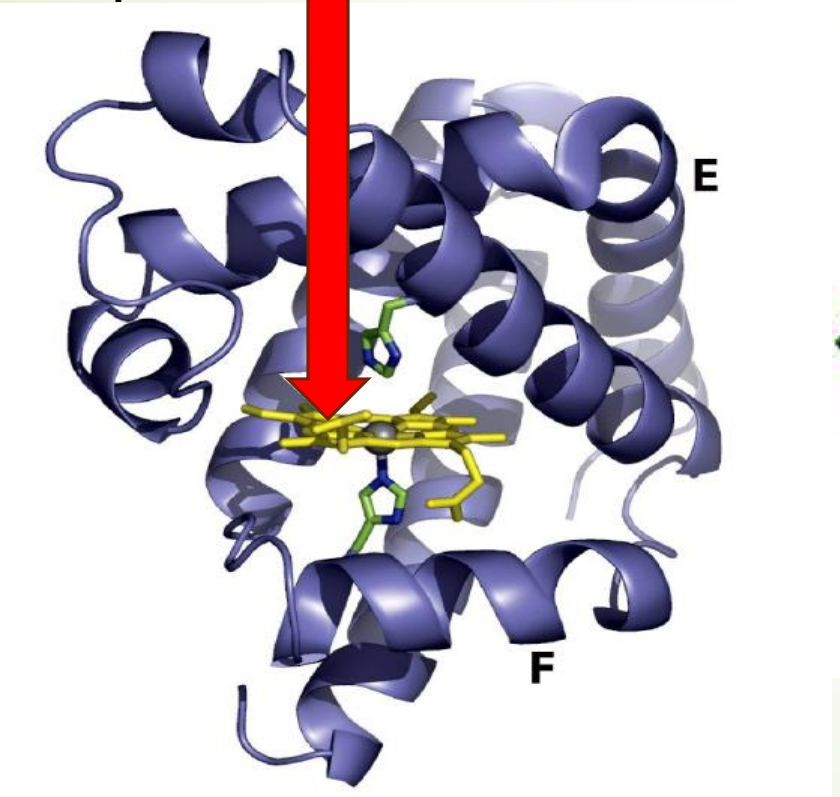

Natural Oxygen Carriers
Heme Containing Proteins, Hb, Mb
Hemocyanin
Hemerythrin

Structure of a metallo-protein : A metal complex perspective

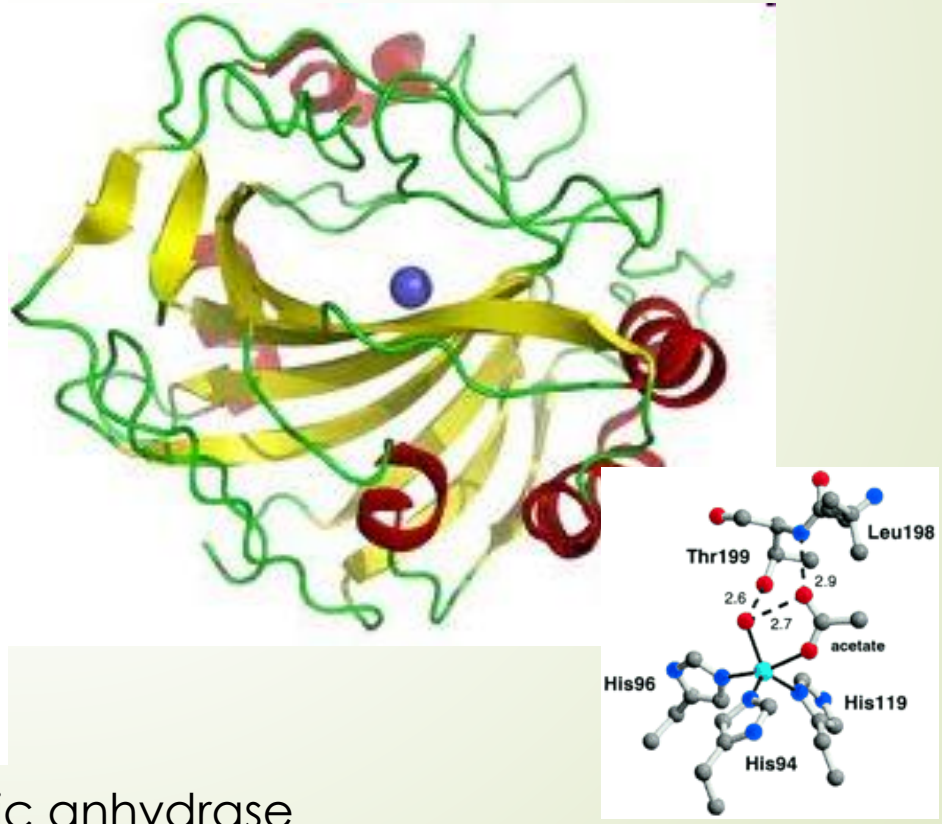
Spiral - α helix form of protein Tape - β Pleated sheet form of protein

Prosthetic groups – A metal complex positioned in a crevice. Some of the ligands for this comp x or some times all of the ligands are provided by the side groups of the amino cid units.

The geometry around the metal and bond distances and angles are decided by the protein ur



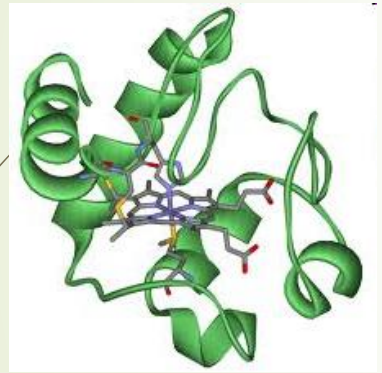
Myoglobin



Carbonic anhydrase

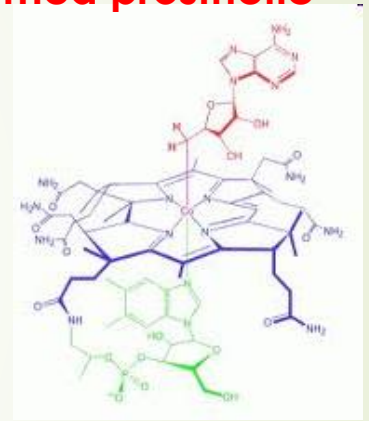
Metalloenzymes and Oxygen carriers
= Protein + Cofactor

A **cofactor** is a non-protein chemical compound that is bound to a protein and is required for the protein's biological activity. These proteins are commonly **enzymes**. Cofactors are either organic or inorganic. They can also be classified depending on how tightly they bind to an enzyme, with loosely-bound or protein-free cofactors termed **coenzymes** and **tightly-bound cofactors termed prosthetic groups.**

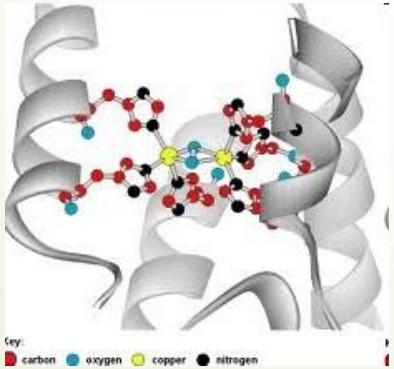


Cytochrome C

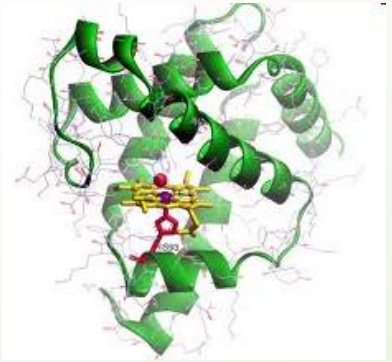
Porphyrins with different metals at its centre are a common prosthetic group in bioinorganic chemistry



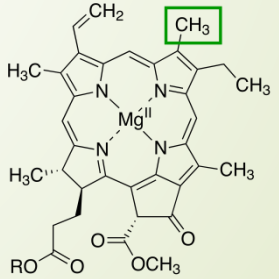
Coenzyme B12



Hemocyanin



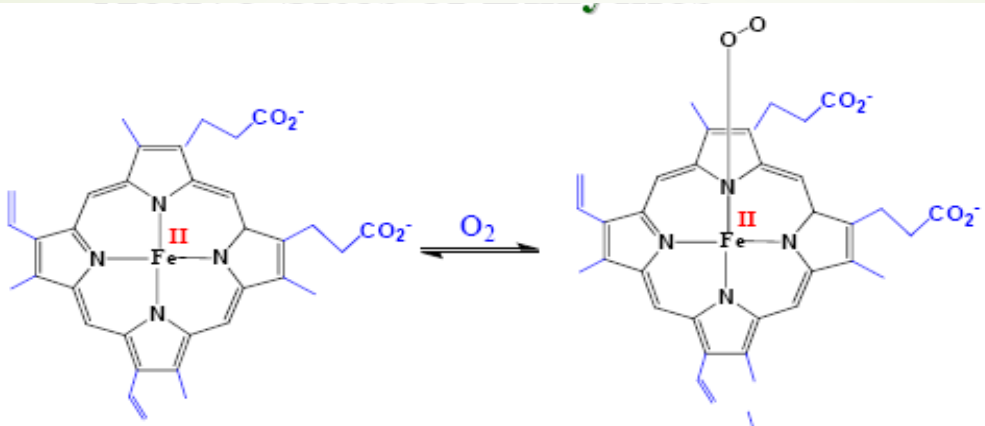
Myoglobin



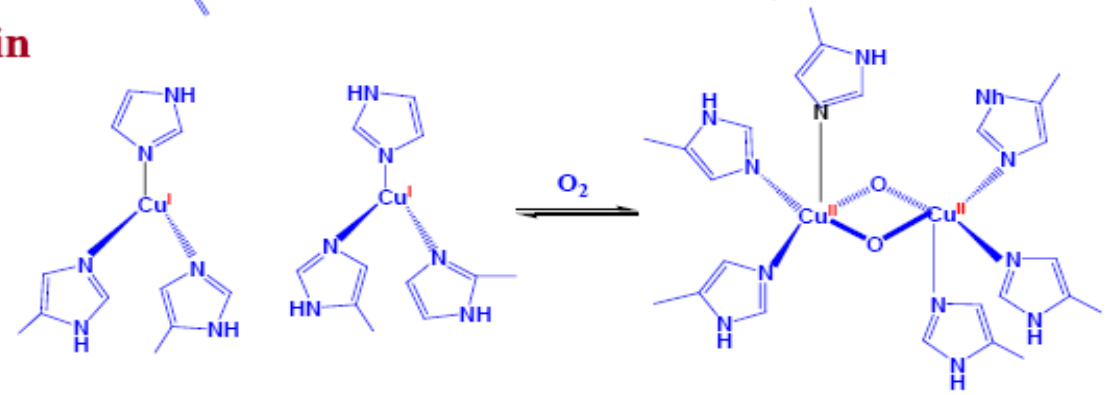
Chlorophyll

Inorganic Prosthetic group of three well known oxygen carriers

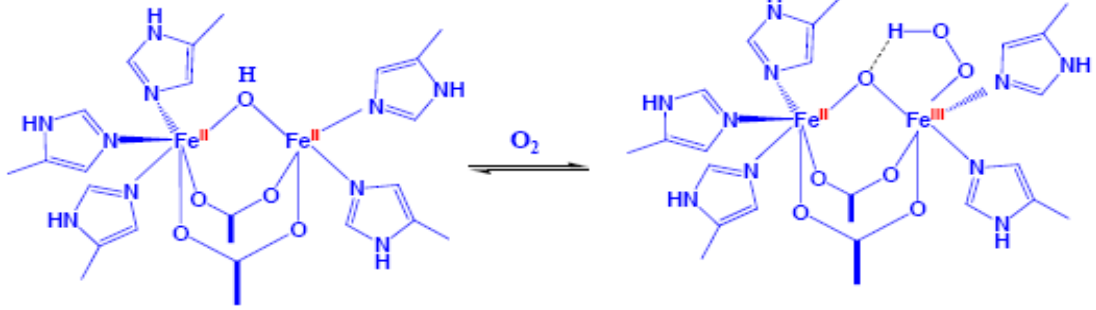
Hemoglobin



Hemocyanin



Hemerythyrin

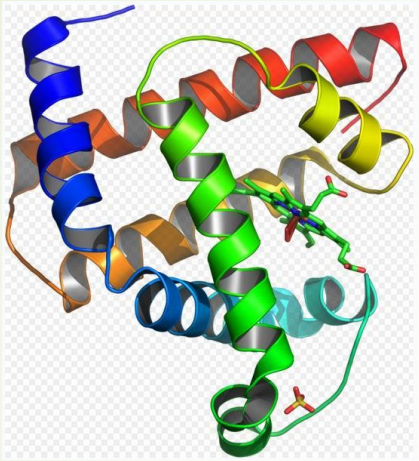


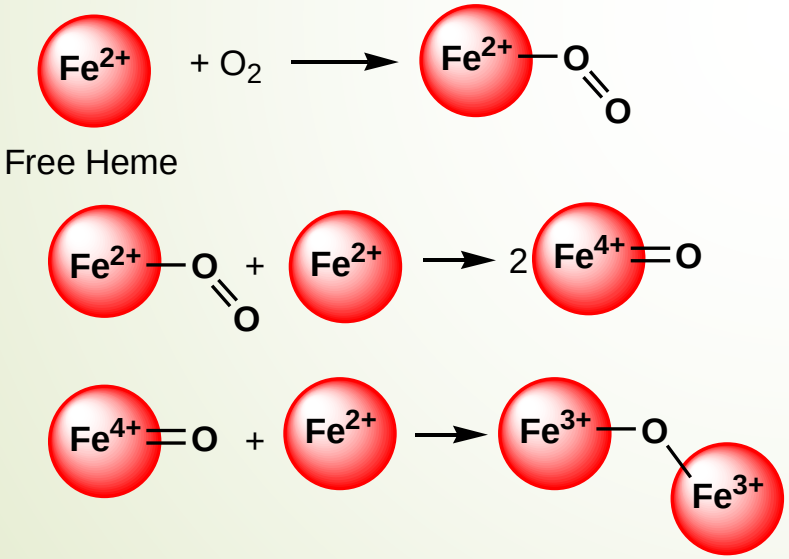
Present in Vertebrates

Present in molluscs

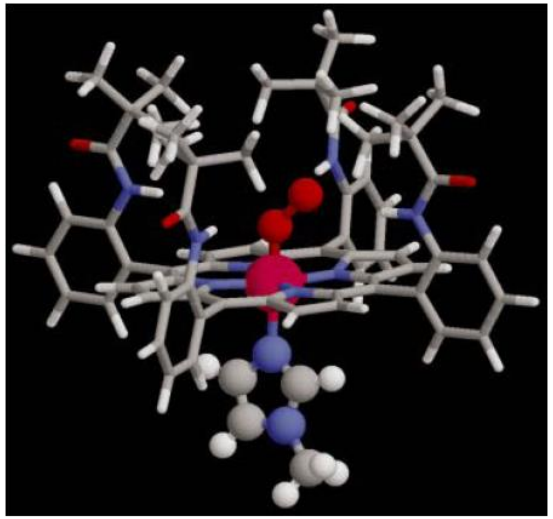
Present in some sea worms

Can the prosthetic unit part of a metalloprotein perform its normal function without the protein unit around it ?





picket fence porphyrin



Reversible binding of O_2 is possible on when protein unit is present around the heme unit

Natural oxygen carriers

Oxygen Carriers	Metal	Mole Ratio O_2/metal	Function	Ligand
HEMOGLOBIN	Fe (II)	1/1	Carrier	Porphyrin
MYOGLOBIN	Fe (II)	1/1	Storage	Porphyrin
HEMERYTHRIN	Fe (II)	1/2	Carrier	Protein
HEMOCYANIN	Cu (I)	1/2	Carrier	Protein

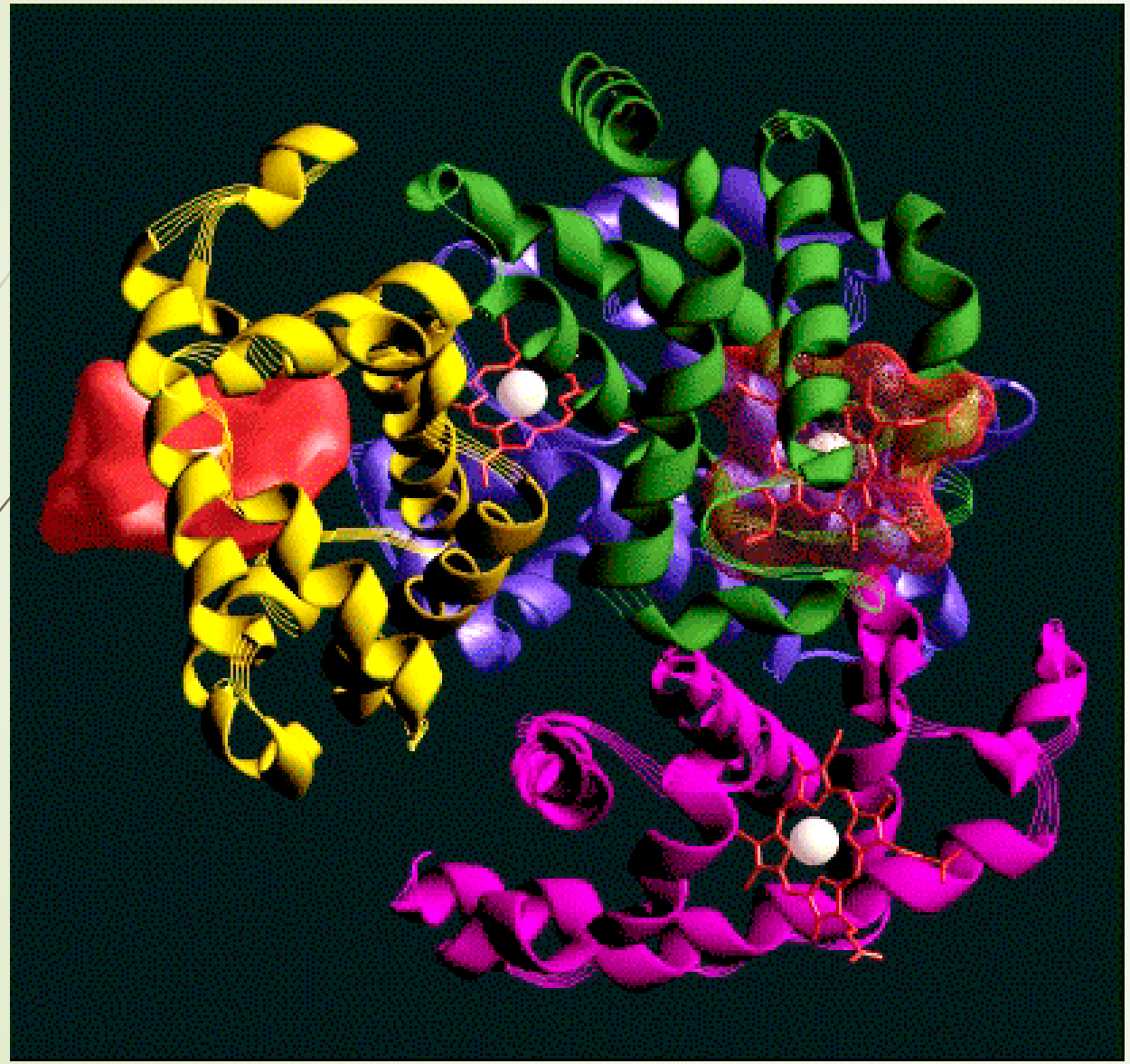
Comparison of the various oxygen transport proteins

Property	hemoglobin	hemerythrin	hemocyanin
Metal ion	Fe^{II}	Fe^{II}	Cu^{I}
Number of subunits	4	8	10 – 100
M	65.000	108.000	450.000 – 10 000 000
M:O_2 ratio	1:1	2:1	2:1
Colour (deoxy)	purply-red	colourless	colourless
Colour (oxy)	bright red	violet-pink	blue
Metal bindig site	porphin	protein	protein

General features of dioxygen-carrier proteins.

Metalloprotein	Active site of deoxy	Color change deoxy → oxy	MW (Dalton)	# Subunits	Average MW subunit (Dalton)
Hemoglobins					
Vertebrate					
Human A	heme Fe^{II}	purple → red	64,000	4	16,000
Invertebrate					
Erythrocruorin (*Lumbricus terrestris*, earthworm)	heme Fe^{II}	purple → red	up to 3.3×10^6	192	17,000
Chlorocruorin (*Eudistylia vancouveri*)	chloroheme Fe^{II}	purple → green	3.1×10^6	192	15,000
Hemocyanins					
Mollusc (*Helix pomatia-α*, edible snail)	Cu^{I} . . . Cu^{I}	colorless → blue	$\sim 9 \times 10^6$	160	52,700
Arthropod					
(*Cancer magister*, crab)	Cu^{I} . . . Cu^{I}	colorless → blue	$\sim 9 \times 10^5$	12	76,600
Hemerythrins					
(*Phascolopsis* syn. *golfingia gouldii*)	Fe^{II} . . . Fe^{II}	colorless → burgundy	108,000	8	13,500

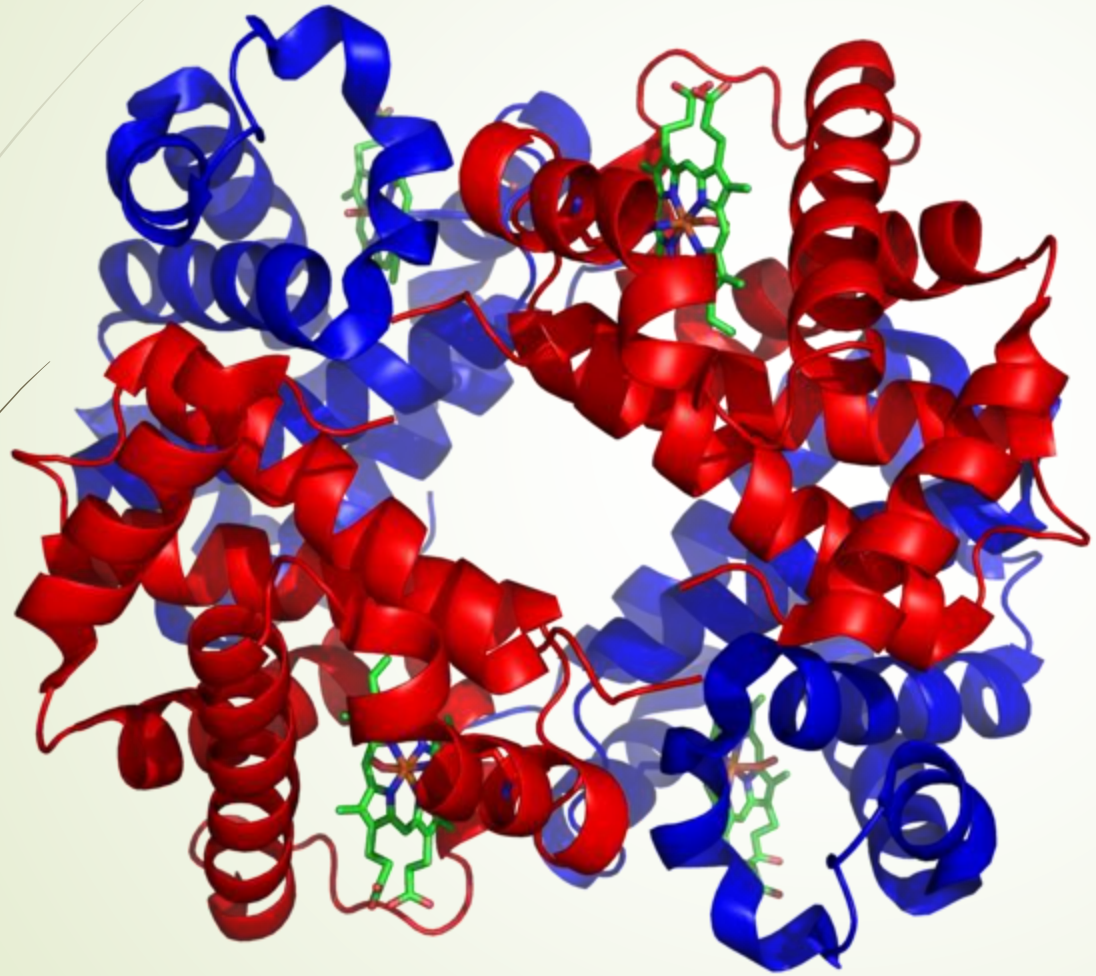
Structure and action of hemoglobin



A complex protein:
Consists of 4 sub-units, each of them being ~ a myoglobin.

The binding between the hem and the protein is similar as in myoglobin.

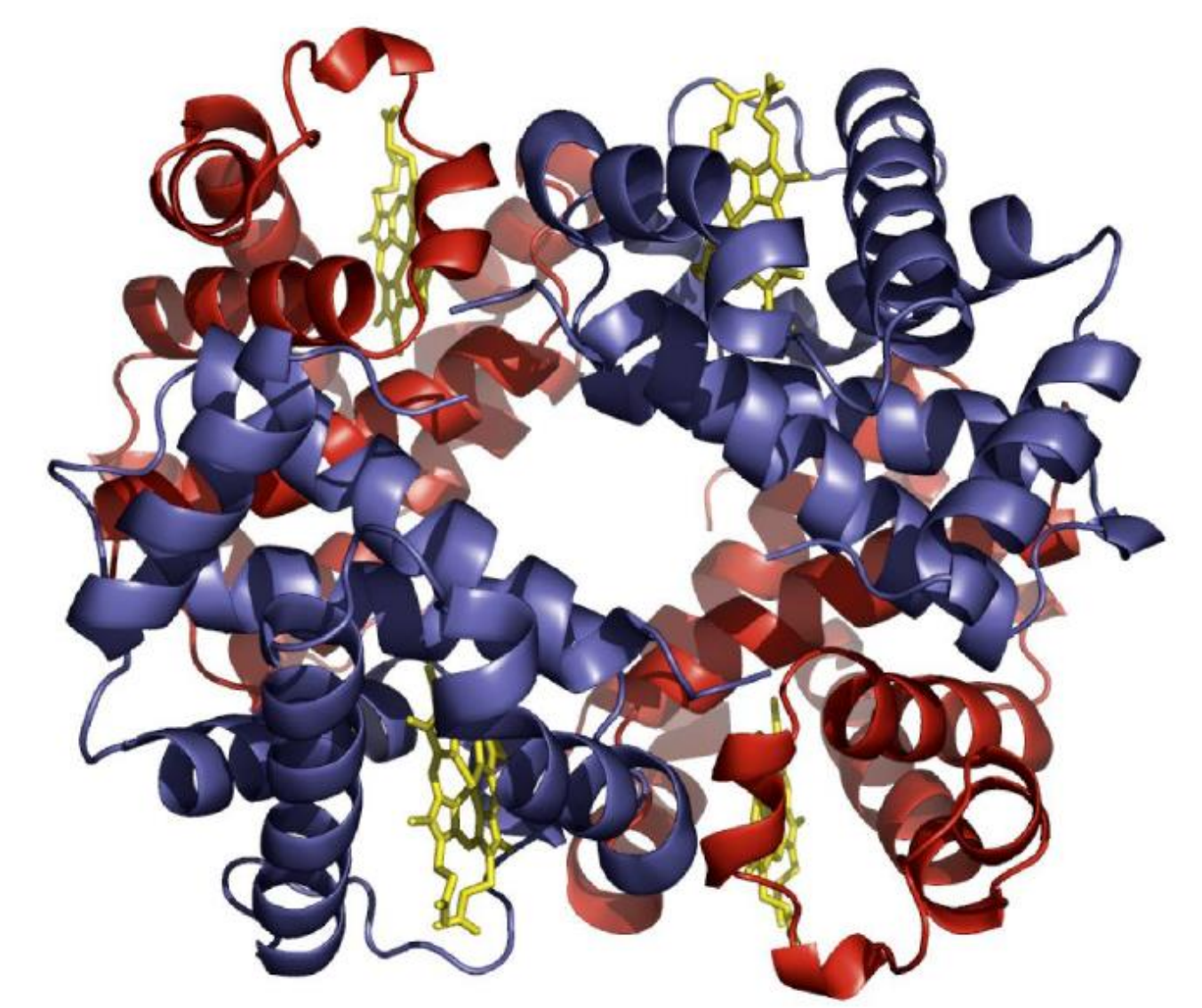
Structure and function of hemoglobin



The protein sub-units are represented by different colours red (2) and blue (2). Hem: green (4)

A Fe^{II} ions are hardly accessible.

Hemoglobin- a quaternary structure of a protein



4 units

Each unit has a prosthetic group (heme) embedded in a crevice and partly coordinated by histidine units

Structure and function of hemoglobin

The oxygen saturation of hemoglobin is characterised by cooperativity: the extent of saturation changes in a ratio of 1:4:24:9 with an increase of the number of bound oxygen molecules .

Reason: The size of the porphyrin ring in case of Fe^{II} complex is not large enough for complete fit; the Fe^{II} ion is above the ring plane closer to the proximal His. Fe^{II} binds more strongly.

During O_2 saturation, there is a reversible electron transfer:

$Fe^{II} + O_2 \rightleftharpoons Fe^{III}\text{-}O_2^-$ *(iron^{III}-superoxo complex)*

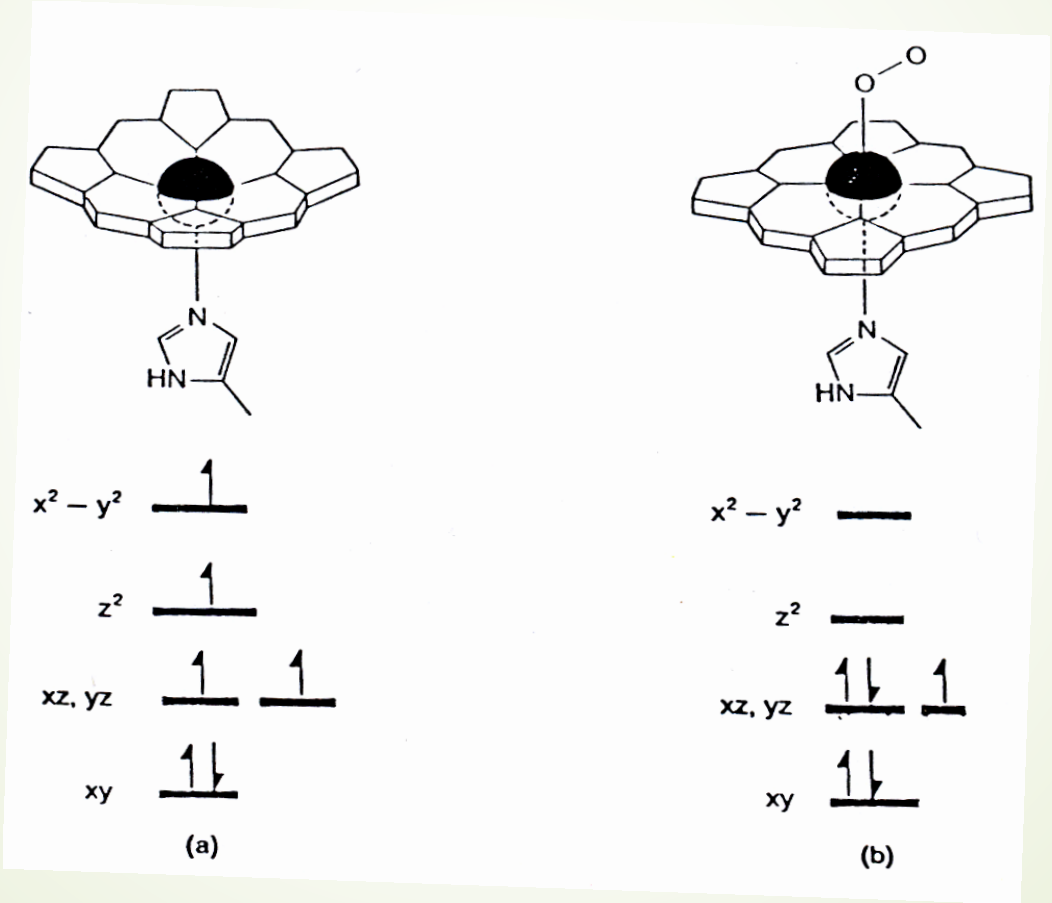
Fe^{III}-ion is smaller, it "falls into" the ring plane and changes the position of the proximal His too.

Binding of superoxo ligand is stabilised by hydrogen-bonding with the distal His.

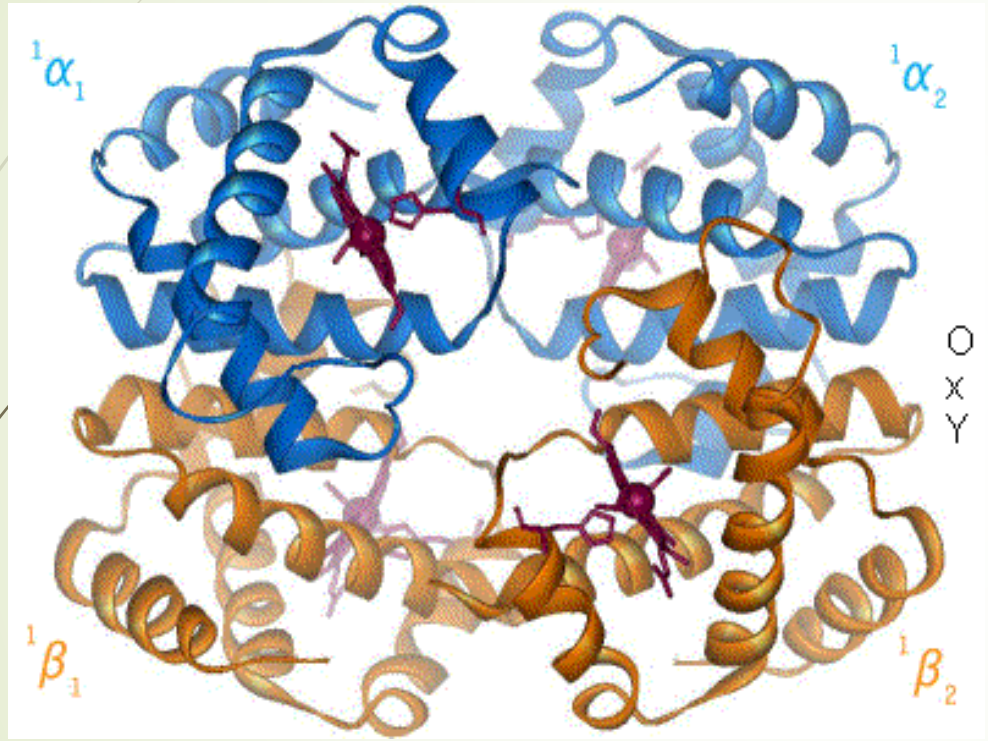
(Movements of the His ligands result in conformational changes in the full molecule. (the molecule becomes "unfolded" for more efficient oxygen binding.)

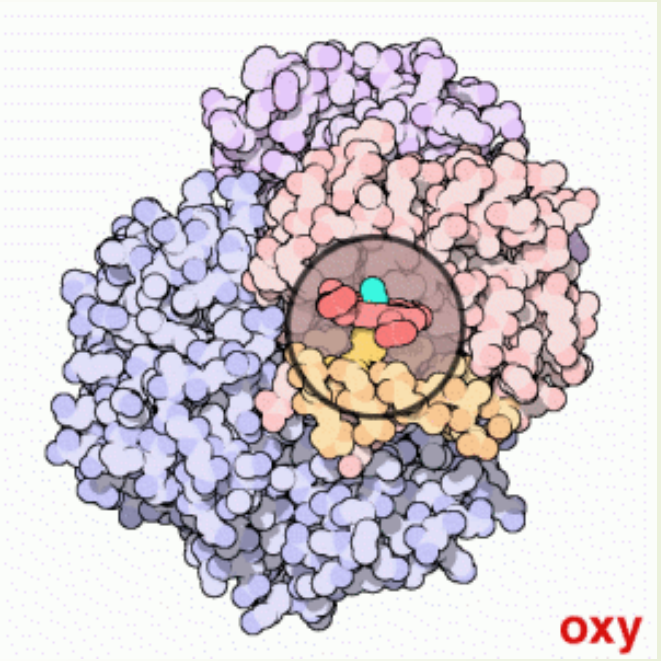
Structure and function of hemoglobin

During binding of oxygen molecule oxidation state and spin state of iron change, which result in the decrease of the size of the ion.



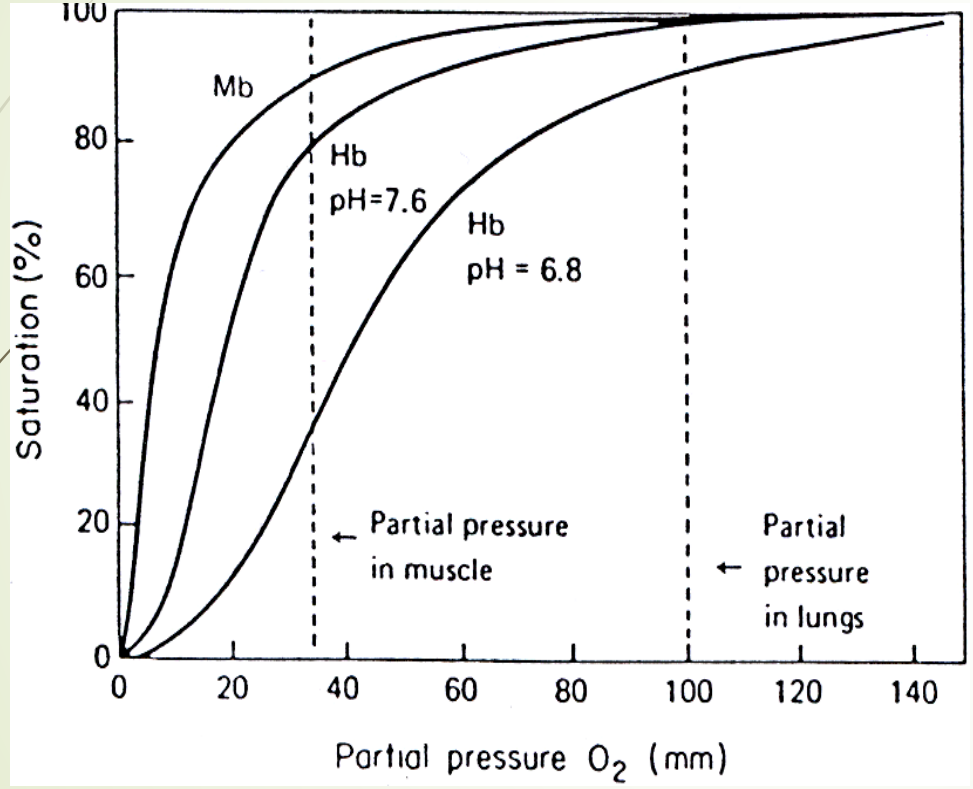
Structure and function of hemoglobin





Structure and function of hemoglobin

Oxygen saturation of hemoglobin is influenced by the pH too.



The increasing muscle activity increases the production of CO_2 , resulting in acidification: at lower pH hemoglobin binds less oxygen providing more for the muscle tissues for the increased physical activity.

$$CO_2 + H_2O \rightleftharpoons HCO_3^- + H^+$$

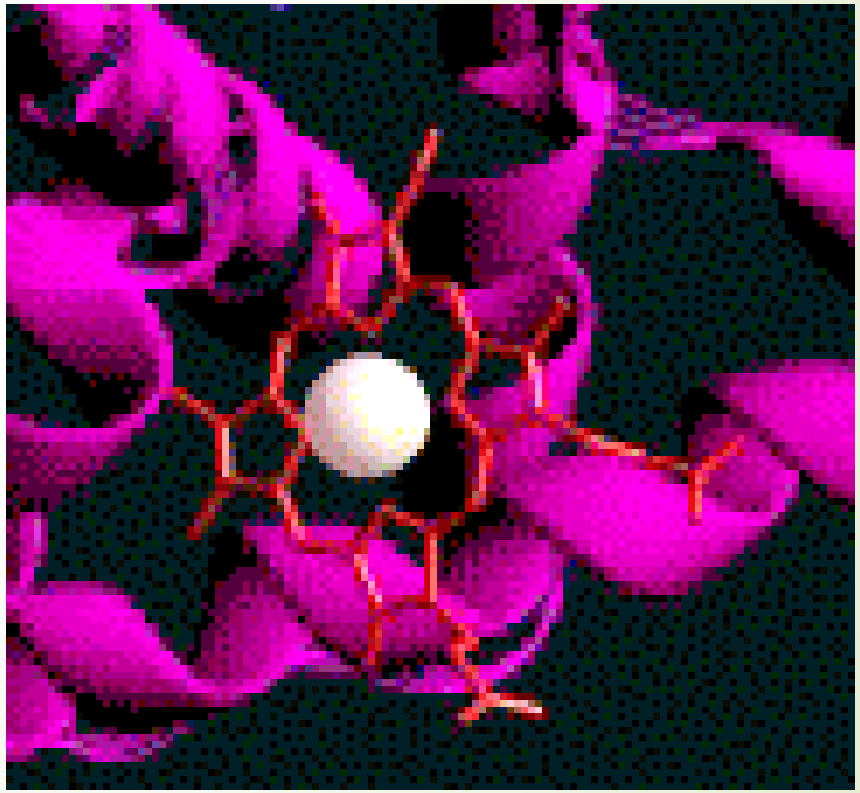
Structure and action of myoglobin

An oxygen storage protein, located in muscle tissue.
It consists of two main parts:

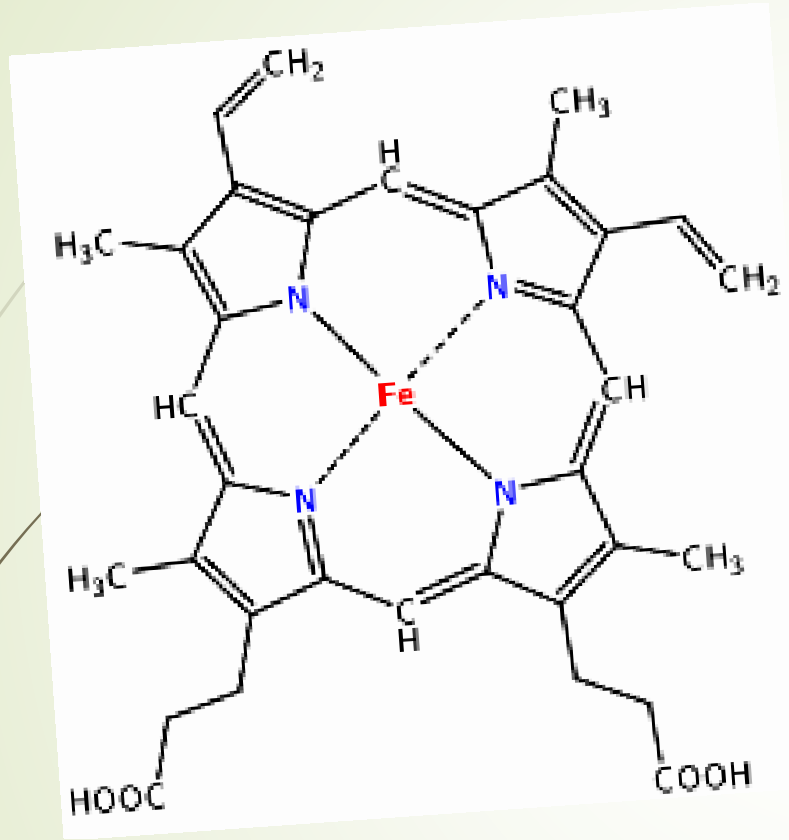
- **protein: globin**
- **prosthetic group: hem**

The globin consists of 153 amino acid molecules.

The 5th coordination position of the octahedral Fe^{II} ion is occupied by a His imidazole-N donor.



Structure and action of myoglobin



hem

Fe^{II} + protoporphyrin IX

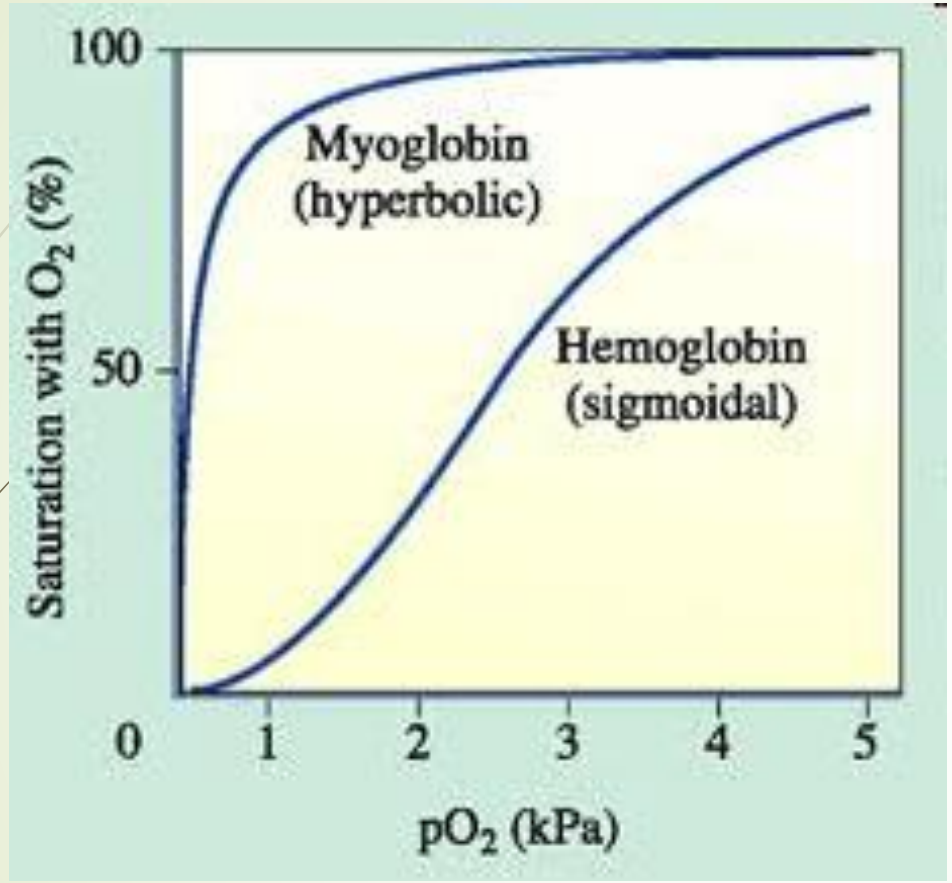
ring: porphin, substituted: porphyrin

The hem binds to the globin part Only via a Fe^{II}-His interaction *(proximal His) without covalent bonds.*

The interaction between the hem and the globin is strengthen by secondary bondings with the globin side chains.

The imidazole-N of another His is (distal His) also close to the 6th free coordination position of the iron.

Structure and action of myoglobin



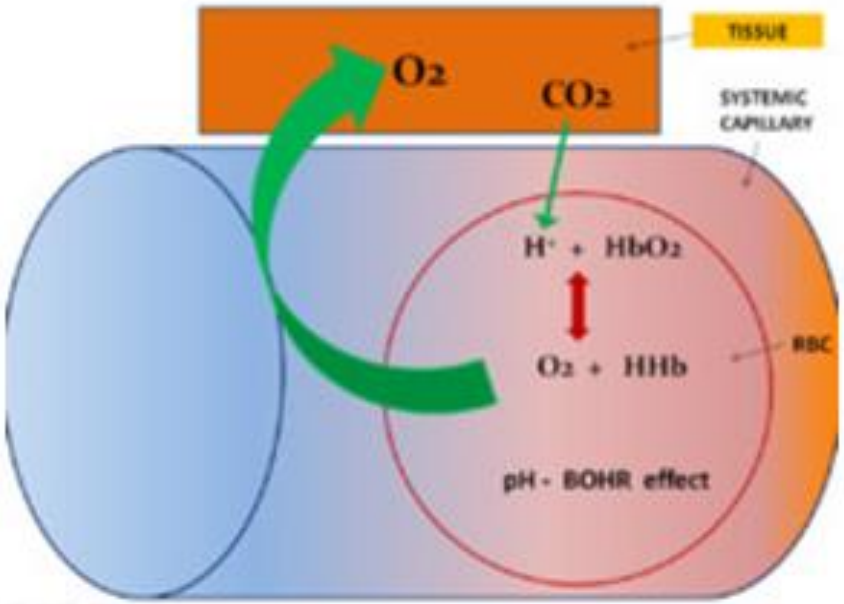
Oxygen saturation curves:

myoglobin:
Saturation, hyper-bolical curve

hemoglobin:
sigmoid curve →
"cooperativity"

In the lung *(p_{O2} > 100 Hgmm)* the hemoglobin is saturated by O_2, while in the muscles, where the partial pressure of O_2 is lower *(~ 40 Hgmm)*, hemoglobin transfers oxygen to myoglobin.

BOHR EFFECT

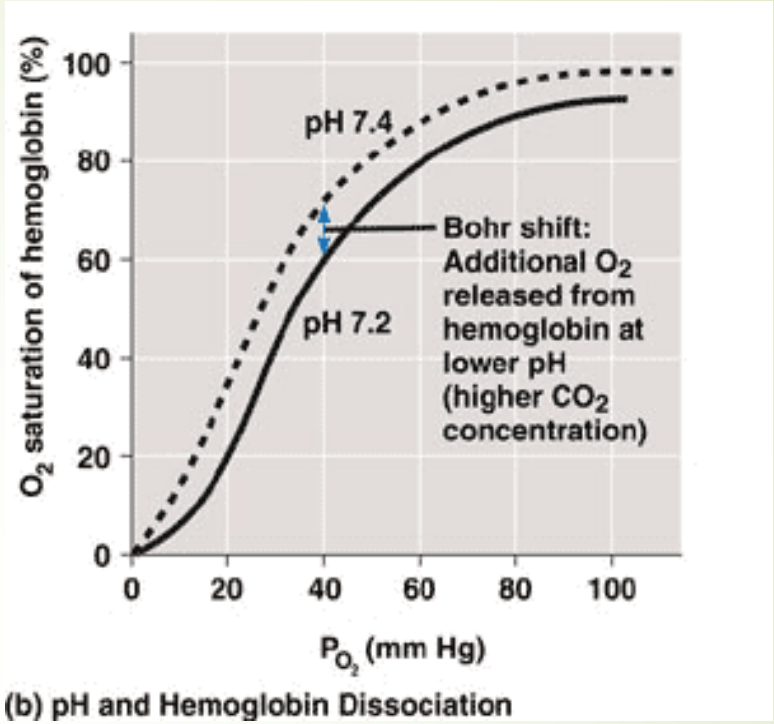


- *The change in oxygen affinity with pH is known as the Bohr effect.*
- *Hemoglobin **oxygen affinity is reduced as the acidity increases**.*

- *The Bohr effect is a manifestation of the acid-base equilibrium of hemoglobin.*
- *The pH-mediated change in affinity for oxygen helps hemoglobin act like a shuttle that picks up oxygen in the lungs and deposits it in the tissues where it will be needed.*

- *Since the tissues are relatively rich in carbon dioxide, the **pH is lower** than in arterial blood; therefore, the Bohr effect **facilitates transfer of oxygen**.*

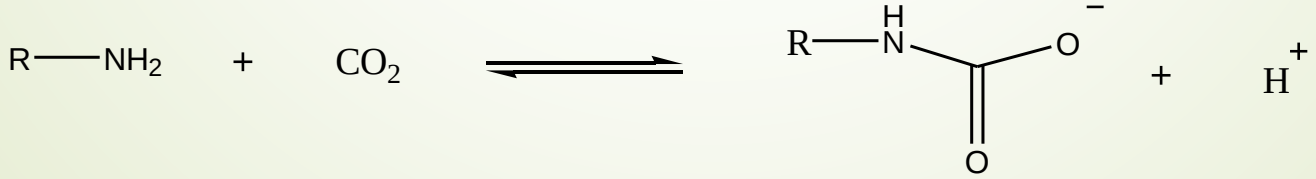
Haemoglobin's oxygen binding affinity is inversely related both to acidity and to the concentration of carbon dioxide. Since carbon dioxide reacts with water to form carbonic acid, an increase in CO_2 results in a decrease in blood pH, resulting in haemoglobin proteins releasing their load of oxygen. Conversely, a decrease in carbon dioxide provokes an increase in pH, which results in haemoglobin picking up more oxygen.



(b) pH and Hemoglobin Dissociation

CO_2 binding with Hb

CO2 carried by Hb in the form of carbamate due to reaction of unionised amino groups of Hb with CO2 and form carbamates, these carbamates forms salt bridges which stabilize the Tensed (T) state or deoxygenated form.



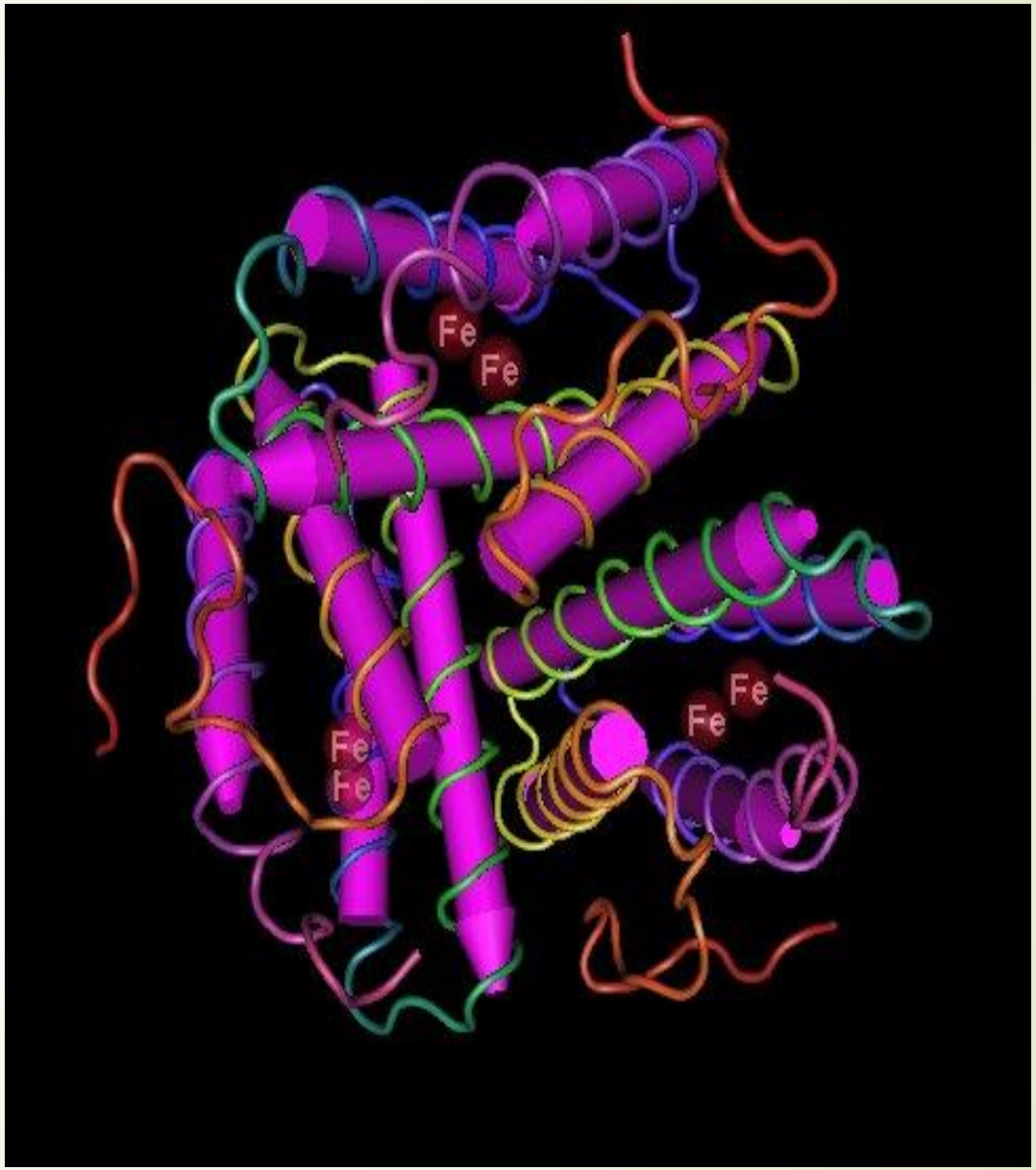
Carbamate

Hemerythrin

Several other iron containing proteins (e.g. hemerythrin and ribonucleotide reductase) contains oxo- or hydroxo bridged dimeric units.

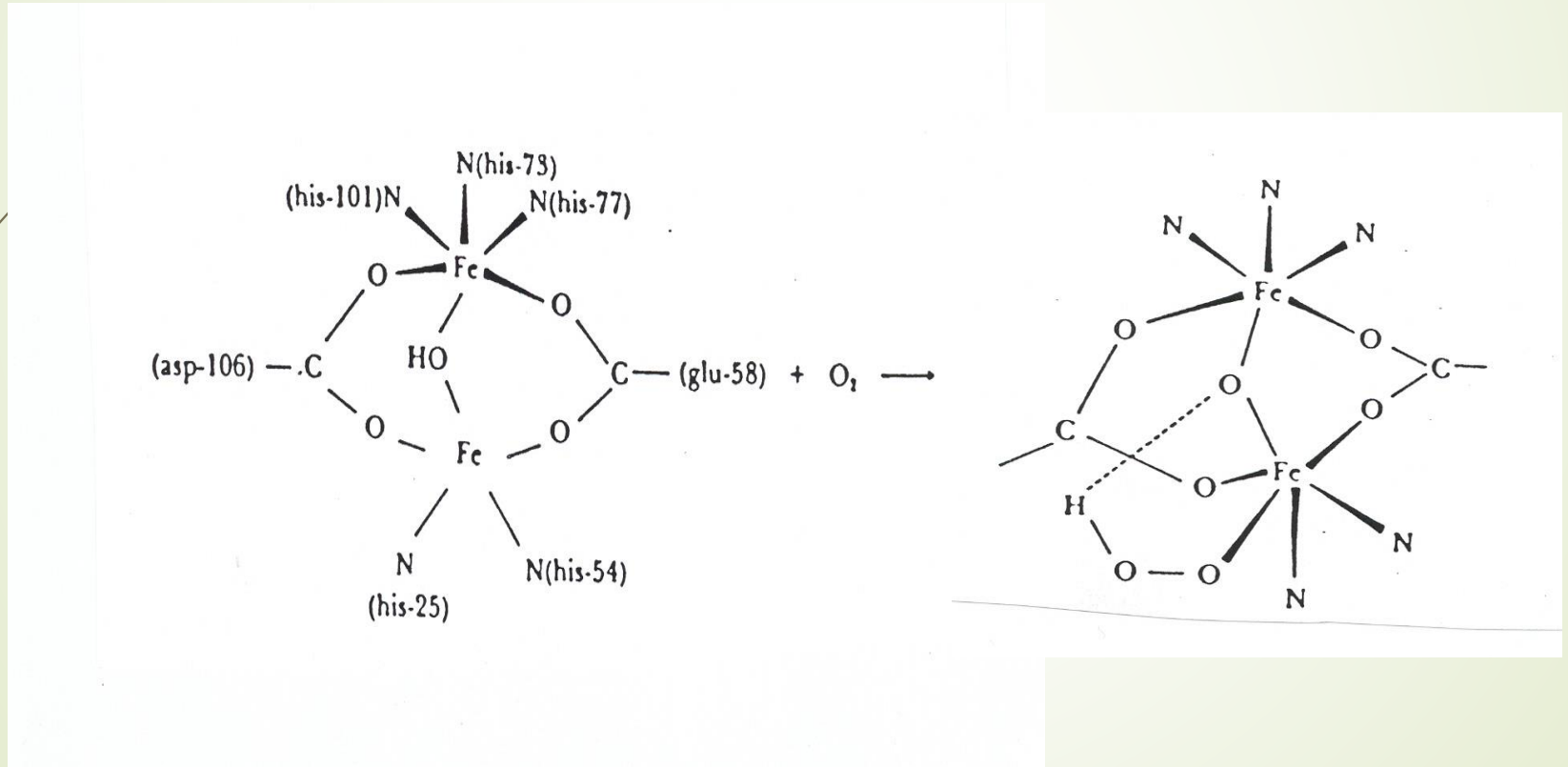
Hemerythrin consists of max. 4 subunits *(the figure shows a trimer)*. Each subunit contains two Fe(II) ions and binds one O_2.

Oxygen carrier molecule in some lower animals *(e.g. marine worms)*.



Hemerythrin

In resting state it contains hidroxo and carboxylate bridged Fe^{II}-ions. One of the Fe^{II} ions is unsaturated coordinatively and thus behaves as O_2 binding site. The Fe^{II} ions are oxidised to Fe^{III} the peroxo group is stabilised by hydrogen-bonding too. (The reversibility is not complete.)



Hemocyanin

Function:

Oxygen transporter of several groups of invertebrates
(e.g. octopus, lobster, snails, spiders, etc.)

Structure: **complex protein → M ~ 450 000 - 9 000 000**
It consists of 10 - 100 subunits. M ~ 50-70 kDa/subunit

Copper content: **2 copper/subunit**

Mechanism of Oxygen binding:

$$[Cu(I)]_2 + O_2 \rightleftharpoons [Cu(II)-O_2^{2-}-Cu(II)]$$

deoxy: Cu(I), ***oxy: Cu(II)-peroxo***
Colourless, diamgnetic ***blue/green, diamagnetic***

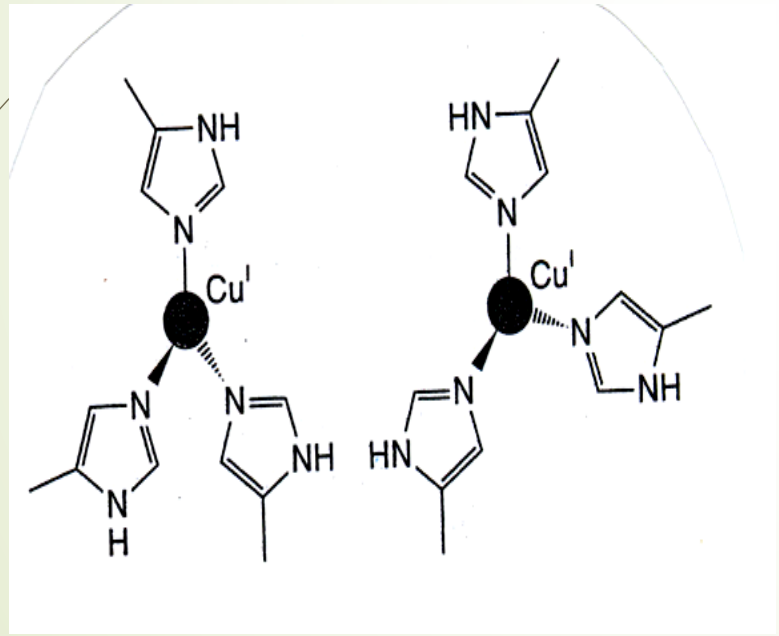
In acidic media the reaction becomes irreversible:

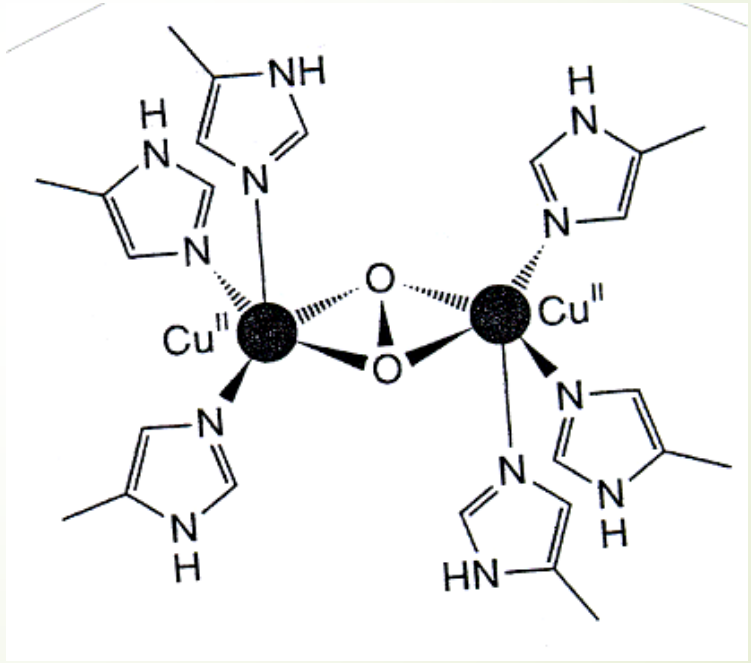
$$[Cu(II)\text{-}O_2^{2-}\text{-}Cu(II)] + 2H^+ \rightarrow [Cu(II)]_2 + H_2O_2$$

Hemocyanin

Binding modes in the deoxy- and oxyhemocyanin
Cu–Cu distances:

deoxy: 460 pm **oxy: 354 pm**





Format: Abstract Send to

Curr Opin Investig Drugs. 2002 Aug;3(8):1187-90.

Oxygen carriers.

Chang TM[1].

Author information

Abstract

Three polyhemoglobins, formed by intermolecular cross-linking of hemoglobin molecules are in advanced phase III clinical trials and two conjugated hemoglobins, formed by cross-linking of hemoglobin molecules with soluble polymer, are also undergoing clinical trials. A perflubron-based emulsion is undergoing phase III clinical trials and a new recombinant human hemoglobin that does not bind to nitric oxide is also being developed. New oxygen carriers with antioxidant properties are being developed for conditions with potential for ischemia-reperfusion injuries. Third generation oxygen carriers are based on microencapsulation of hemoglobin and red blood cell enzymes either in liposomes or in biodegradable nanocapsules. This review will briefly discuss lessons learnt from the past, give an overview on the current status of selected oxygen carriers and discuss research areas in need of further development.

PMID: 12211412

[Indexed for MEDLINE]

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ELSEVIER

Side Effects of Drugs Annual

Volume 33, 2011, Pages 669-690

Chapter 33 - Blood, blood components, plasma, and plasma products

P.F.W. Strengers, K.J. Velthove

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https://doi.org/10.1016/B978-0-444-53741-6.00033-7

Publisher Summary

This chapter presents the studies of the effects of blood, blood components, plasma, and plasma products. The use of 20% albumin infusion in the treatment of neonatal hypoalbuminemia is controversial because of the lack of evidence-based guidelines. In a retrospective study of 30 neonates, no adverse effects of albumin infusion have been registered. Heparin increases the risk of bleeding in patients who are receiving drotrecogin. In a double- blind, randomized, placebo-controlled trial of prophylactic heparin in patients with severe sepsis treated with drotrecogin 24 micrograms/kg/hour for 96 hours, patients were randomized to unfractionated heparin 5000 units bd, enoxaparin 40 mg/day, or placebo every 12 hours. There were more bleeding events overall during the infusion of drotrecogin in those who also received heparin compared with placebo, but serious bleeding events were similar and central nervous system bleeds were uncommon in both groups.

Previous chapter in volume

Next chapter in volume

℞ The risks of infections from transfusions

The administration of blood, blood components, plasma, and plasma products always carries the potential risk of transmission of infectious agents [1R,2R]. Owing to increased standards of donor screening, serological testing, and nucleotide amplification testing (NAT),

Part of volume:

A worldwide yearly survey of new data in adverse drug reactions

Edited by J.K. Aronson

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Side Effects of Drugs Annual
Volume 39, 2017, Pages 331-343

Chapter 29 - Blood, Blood Components, Plasma, and Plasma Products

Maria Cardinale *, †, Kent Owusu ‡, Tamara Malm ‡, §

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https://doi.org/10.1016/bs.seda.2017.06.011

Abstract

This review of the 2016 publications on important side effects of blood, blood components, plasma, and plasma products covers albumin, blood transfusion (erythrocytes, granulocytes, and platelets), blood substitutes (hemoglobin-based oxygen carriers), plasma products (alpha1-antitrypsin, C1 esterase inhibitor concentrate, cryoprecipitate, and fresh frozen plasma), plasma substitutes (dextrans, etherified starches, and gelatin), globulins (intravenous immunoglobulin, subcutaneous immunoglobulin, and anti-D immunoglobulin), coagulation proteins (factor I, factor II, factor VIIa, factor VIII, factor IX, prothrombin complex concentrate, antithrombin III, and von Willebrand factor/factor VIII concentrates), erythropoietin and derivatives, thrombopoietin and receptor agonists, transmission of infectious agents through blood donation, and stem cells.

This chapter includes blood products for which hemovigilance is in force and allows the reader to stay up to date on newly recognized and published data in the blood product arena. Since blood and plasma products are available through blood donation, prevention of transmitted infections is of extreme importance and is also discussed here.

Previous chapter in volume

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Keywords

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Side Effects of Drugs Annual

Volume 35, 2014, Pages 583-605

Chapter 33 - Blood, blood components, plasma, and plasma products

K.J. Velthove, P.F.W. Strengers

https://doi.org/10.1016/B978-0-444-62635-6.00033-4

Abstract

The Side Effects of Drugs Annuals form a series of volumes in which the adverse effects of drugs and adverse reactions to them are surveyed. The series supplements the contents of Meyler's Side Effects of Drugs: the International Encyclopedia of *Adverse Drug Reactions* and Interactions. This review of the 2011 publications on adverse reactions to blood, blood components, plasma, and plasma products covers albumin, blood transfusion (erythrocytes and platelets), blood substitutes (hemoglobin-based oxygen carriers), plasma products (C1 esterase inhibitor concentrate and fresh frozen plasma), plasma substitutes (dextrans, etherified starches, and gelatin), globulins (intravenous immunoglobulin, subcutaneous immunoglobulin, and anti-D immunoglobulin), coagulation proteins (factor VIIa, factor VIII, factor IX, prothrombin complex concentrate, and von Willebrand factor/factor VIII concentrates), erythropoietin and derivatives, and stem cells. This includes blood products for which hemovigilance is in force, plasma products that must comply with pharmacovigilance regulations, substitute products, and stem cells. Because blood and plasma products originate from human blood through blood donation, prevention of transmitted infections (by, for example, bacteria, viruses, protozoa, and prions) form the use of blood, blood components, plasma, and plasma-derived medicinal products is of paramount importance. Nowadays, the risk of transmission of the lipid-enveloped viruses, human immunodeficiency virus (HIV), hepatitis C virus (HCV) and hepatitis B virus (HBV) by plasma-derived medicinal products is considered negligible.

Outline

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Side Effects of Drugs Annual

Volume 32, 2010, Pages 591-606

33 - Blood, blood components, plasma, and plasma products

P.F.W. Strengers, Ch. P. Pescott

https://doi.org/10.1016/S0378-6080(10)32033-2

Publisher Summary

This chapter discusses the adverse effects of blood, blood components, plasma, and plasma products on human physiology. In a prescription monitoring study in three hospitals of 187 patients who received 426 prescriptions for a total of 21 094 g of albumin for hypoalbuminaemia, plasmapheresis, and ascites or hepatorenal syndrome, no adverse events were attributed to albumin. Hemorrhage is a potentially serious adverse effect of drotrecogin, an anticoagulant proteins. Blood component transfusion, including erythrocyte concentrates, platelet concentrates, and fresh frozen plasma, is associated with adverse effects, some of which are severe or even lethal. Recent reports of several national hemovigilance offices include febrile non-hemolytic transfusion reactions, acute hemolytic transfusion reactions, delayed hemolytic transfusion reactions, transfusion-related acute lung injury, post-transfusion purpura, transfusion-associated graft-versus-host disease, acute allergic and anaphylactic reactions, other allergic reactions, transfusion-associated circulatory overload, viral infections, bacterial contamination, hemosiderosis, and new allo-antibody formation.

Previous chapter in volume

Next chapter in volume

Albumin *(SED-15, 54; SEDA-29, 338; SEDA-30, 381; SEDA-31, 527)*

Part of volume:

Side Effects of Drugs Annual 32: A worldwide yearly survey of new data and trends in adverse drug reactions and interactions

Edited by J.K. Aronson

Outline

ELSEVIER

Side Effects of Drugs Annual
Volume 34, 2012, Pages 509-529

33 - Blood, blood components, plasma, and plasma products

K.J. Velthove, P.F.W. Strengers

https://doi.org/10.1016/B978-0-444-59499-0.00033-7

Abstract

This chapter will provide information on reported side effects in the literature published during the year 2010 with regard to different types of blood and plasma products and alternatives. Firstly, safety of blood and plasma transfusion will be discussed where the focus will be on the risk of TRALI development. For these products hemovigilance is in force. Secondly, plasma products will be discussed which must comply with pharmacovigilance regulations. Examples of such products are albumin, C1-esterase inhibitor, immunoglobulins, and coagulation factors. Thirdly, substitute products like hemin, hemoglobin-based oxygen carriers, dextrans, gelatin, etherified starches, erythropoietin and derivatives will be discussed. The safety of stem cell transplantation will be briefly described. Because blood and plasma products originate from human blood through blood donation, the viral safety of blood, blood components, plasma, and plasma-derived medicinal products is of paramount importance. Nowadays, the risk of transmission of the lipid-enveloped viruses human immunodeficiency virus (HIV), hepatitis C virus (HCV) and hepatitis B virus (HBV) by plasma-derived medicinal products is considered negligible.

Previous chapter in volume

Next chapter in volume

Keywords

Blood; Blood components; Plasma; Plasma products; Blood substitutes; Hemovigilance;

Part of volume:

A worldwide yearly survey of new data in adverse drug reactions and interactions

Edited by J.K. Aronson

Oxygen carriers as alternatives to red blood cell transfusion

Author: Joy L Fridey, MD
Section Editor: Arthur J Silvergleid, MD
Deputy Editor: Jennifer S Tirnauer, MD

INTRODUCTION

Alternatives to red blood cell transfusion have been long-anticipated and sought-after developments in biotechnology and medicine. It is generally understood that a manufactured substance cannot carry out the numerous and complex functions of blood, but terms such as "artificial blood" or "blood substitutes" remain popular with the media and the public. Research efforts have been directed toward products that perform the oxygen-carrying and other transport functions of red blood cells. These products are referred to as oxygen carriers (OCs) or oxygen therapeutics (OTs).

This article will provide historical and clinical background and updates on the status of ongoing clinical protocols [1-3].

Red blood cell transfusion and other aspects of tissue oxygen delivery are discussed separately.

- Indications for transfusion (newborns) – (See "Red blood cell transfusions in the newborn".)
- Indications for transfusion (infants and children) – (See "Red blood cell transfusion in infants and children: Indications".)

Literature review current through: Dec 2018. | **This topic last updated:** Nov 29, 2018.

biomolecules

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Review

Hemoglobin-Based Blood Substitutes and the Treatment of Sickle Cell Disease: More Harm than Help?

Abdu I. Alayash

Laboratory of Biochemistry and Vascular Biology, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, MD 20993, USA; abdu.alayash@fda.hhs.gov; Tel.: +1-240-402-9350

Academic Editor: Jürg Bähler
Received: 16 November 2016; Accepted: 26 December 2016; Published: 4 January 2017

Abstract: Intense efforts have been made by both industry and academia over the last three decades to produce viable hemoglobin (Hb)-based oxygen carriers (HBOCs), also known as "blood substitutes". Human trials conducted so far by several manufactures in a variety of clinical indications, including trauma, and elective surgeries have failed and no product has gained the Food and Drug Administration approval for human use. Safety concerns due to frequent incidences of hemodynamic, cardiac events, and even death led to the termination of some of these trials. Several second generation HBOC products that have been chemically and/or genetically modified (or in some cases ligated with carbon monoxide (CO)) found a new clinical application in conditions as complex as sickle cell disease (SCD). By virtue of higher oxygen affinity (P_{50}) (R-state), and smaller size, HBOCs may be able to reach the microvasculature unload of oxygen to reverse the cycles of sickling/unsickling of the deoxy-sickle cell Hb (HbS) (T-state), thus preventing vaso-occlusion, a central event in SCD pathophysiology. However, biochemically, it is thought that outside the red blood cell (due to frequent hemolysis), free HbS or infused HBOCs are capable of interfering with a number of oxidative and signaling pathways and may, thus, negate any benefit that HBOCs may provide. This review discusses the advantages and disadvantages of using HBOCs in SCD.

Keywords: hemoglobin; blood substitutes; sickle cell disease; heme oxidation

Clinical Chemistry

Research Article | Automation and Analytical Techniques

Detection of Hemoglobin-Based Oxygen Carriers in Human Serum for Doping Analysis: Screening by Electrophoresis

Françoise Lasne, Nathalie Crepin, Michael Ashenden, Michel Audran, Jacques de Ceaurriz

DOI: 10.1373/clinchem.2003.026583 Published January 2004

Abstract

Background: Hemoglobin-based oxygen carriers (HBOCs) have recently been included in the International Olympic Committee and World Anti-Doping Agency lists of substances and methods prohibited in sports. To enforce this rule and deter abuse of HBOCs in elite sports, it is necessary to develop HBOC-specific screening and confirmation tests that are the usual steps in antidoping control analysis.

Methods: We developed a screening method based on electrophoresis of serum samples cleared of haptoglobin (Hp). Four successive steps (immunoprecipitation of Hp, electrophoresis of the cleared serum, Western blotting of the separated proteins, and detection of hemoglobin-related molecules based on the peroxidase properties of the heme moiety), provided electropherograms that could be easily interpreted in terms of the presence of HBOCs. This method was tested with serum samples enriched with various types of HBOCs: polymerized, conjugated, and cross-linked hemoglobins. It was also applied to blood samples collected from 12 healthy volunteers who had been infused with either 30 or 45 g of Hemopure, a glutaraldehyde-polymerized bovine hemoglobin.

Results: The method clearly detected the presence in serum of the various types of HBOCs tested and demonstrated no possible confusion with endogenous hemoglobin that may be present in cases of hemolysis. The test was able to detect Hemopure for 4–5 days after administration of 45 g to healthy individuals.

In this issue

Vol. 50, Issue 2
February 2004
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Synthetic or Artificial Oxygen Carriers

What are AOC's and HBOC's?

- Artificial Oxygen Carriers are a type of red blood cell substitute
- Synthetic molecules that consist primarily of carbon and fluorine atoms
- Have the ability to dissolve significant quantities of oxygen and carbon dioxide
- Improve oxygen transport and oxygen unloading to the tissue
- Alternative to allogeneic* blood transfusions or to improve tissue oxygenation and function of organs with limited oxygen supply
- * *Allogeneic meaning genetically different*
- HBOC is a "Hemoglobin Based Oxygen Carrier"
- Must be approved by the FDA before clinical use because these substances are considered drugs

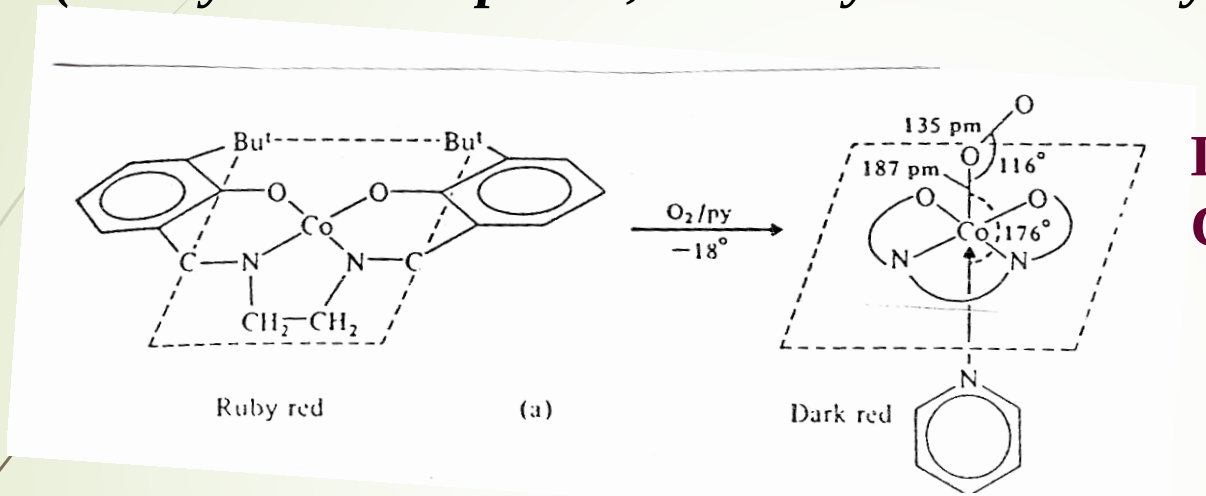
History of AOC/HBOC

- Late 1800's, free hemoglobin solutions were administered
- Modern scientific attempts to replace human blood began in the early 1900's
- HBOC's were created in the 1930's by Amberson
- Modified study by Chang in 1957

- Companies with HBOC'S:
- HemAssist (Phase III Clinical Trials)
- Hemolink (Phase II Clinical Trials)
- OxyVita (Pre-Clinical Trials)

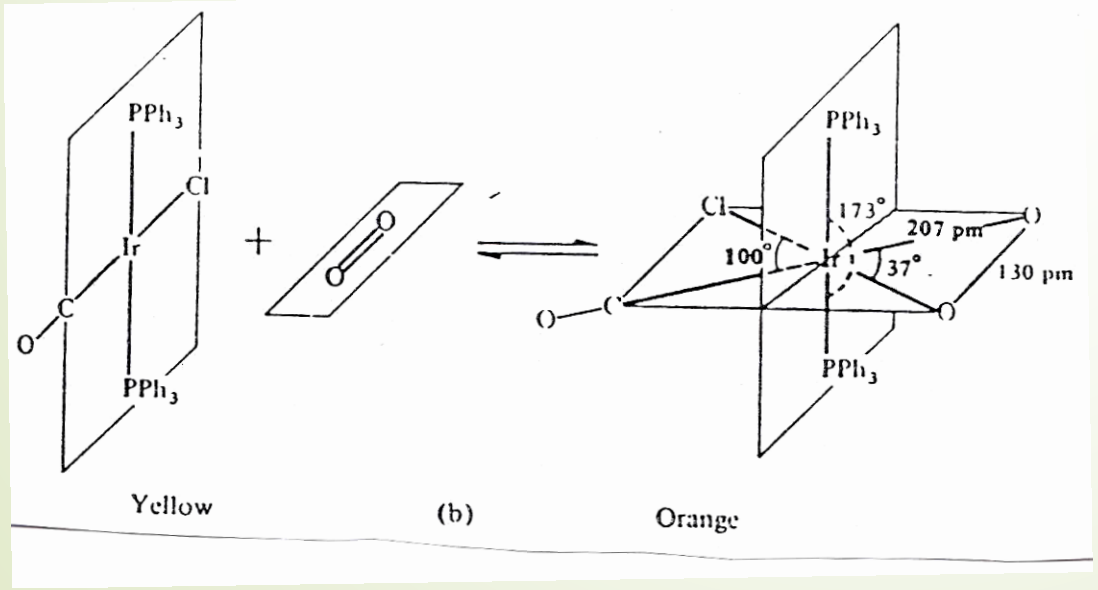
Artificial Oxygen carriers

Reversible binding of O_2 can be achieved by small modell complexes (mostly Co^{II}- complexes, Fe^{II} only with macrocyclic ligands)



L= 3-Bu-Salen

$Co^{II} + O_2 \rightarrow Co^{III}–O_2^-$

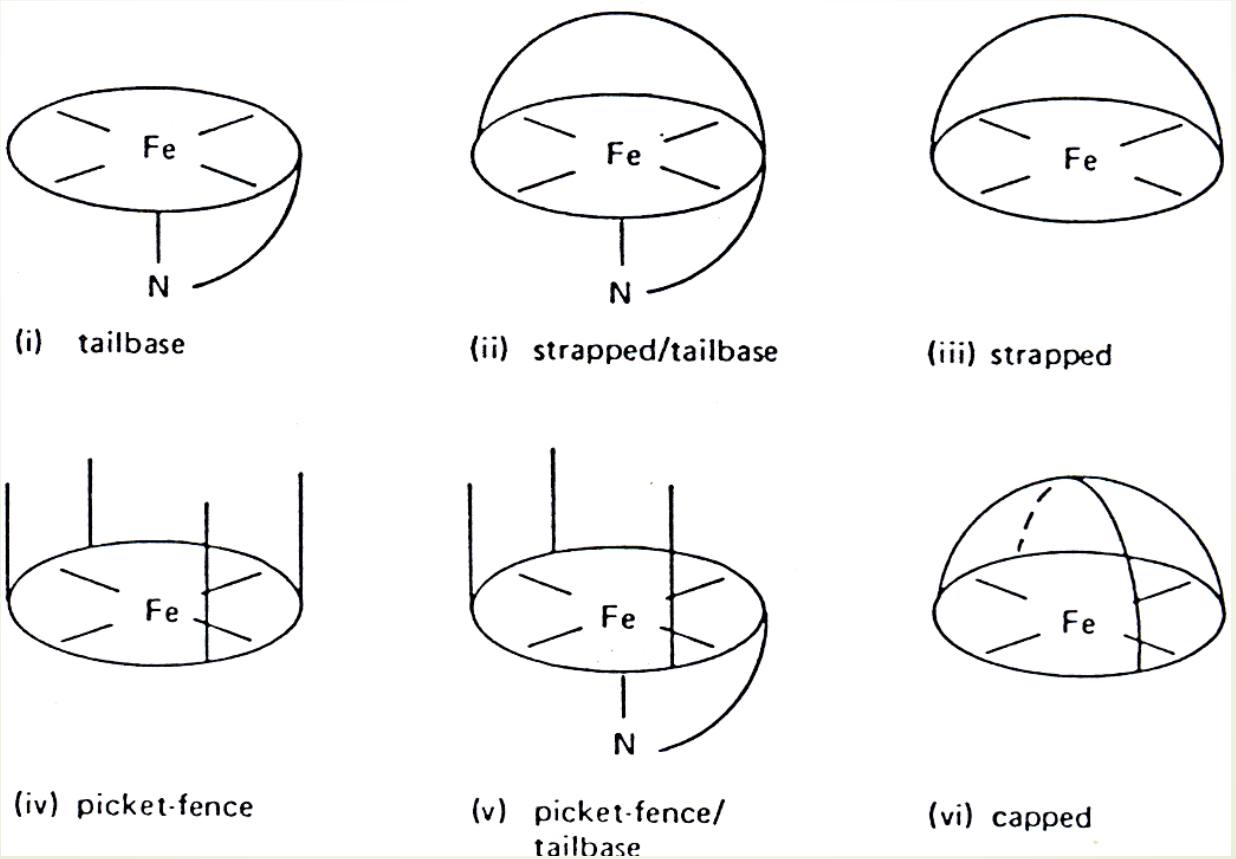


The first synthetic reversible oxygen carrier: Vaska complex $[Ir^I(PPh_3)_2ClCO]$

$Ir^I + O_2 \rightarrow Ir^{III}–O_2^{2-}$

Artificial Oxygen carriers

Reversible oxygen carrier Fe^{II} complexes could be modelled, with N-donor macrocyclic ligands mimicking porphin ring and when the close vicinity of the metal ion was defended by hydrophobic side chains from further mostly redox interactions.



Artificial Oxygen carriers

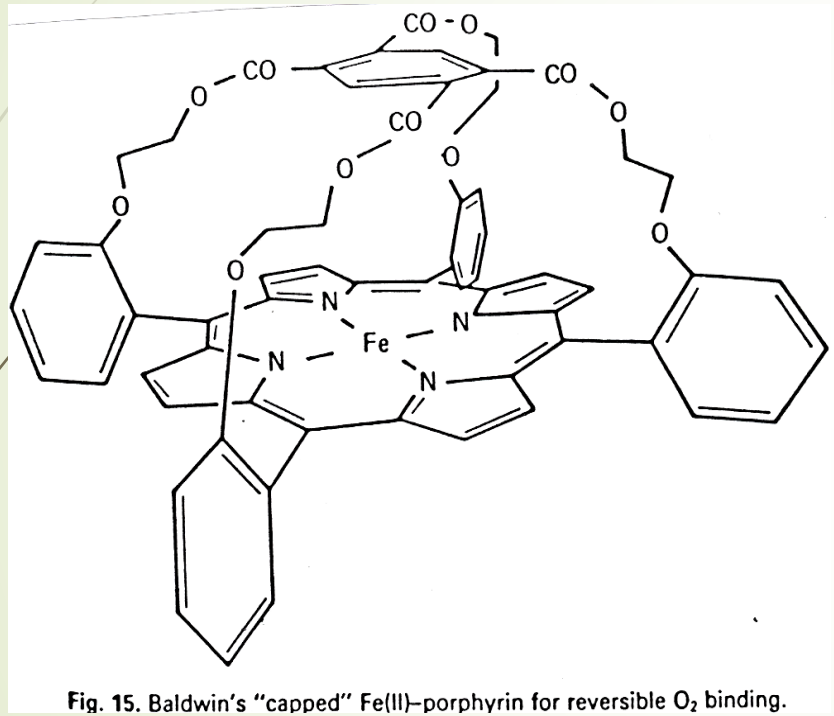


Fig. 15. Baldwin's "capped" Fe(II)–porphyrin for reversible O_2 binding.

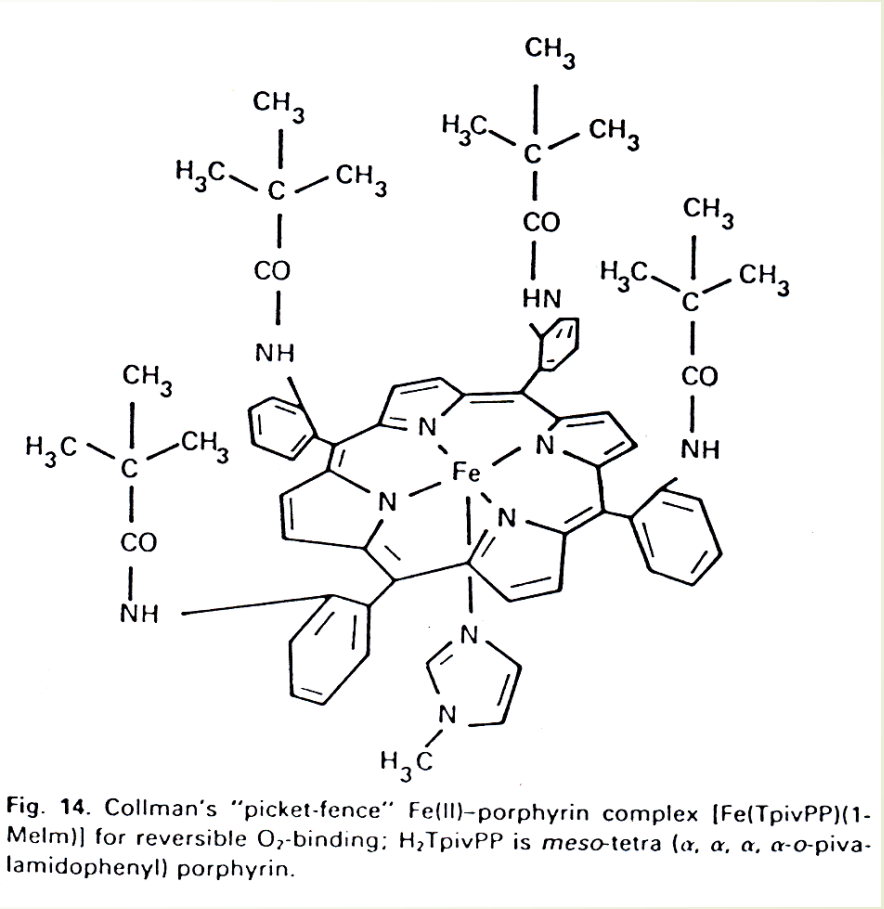
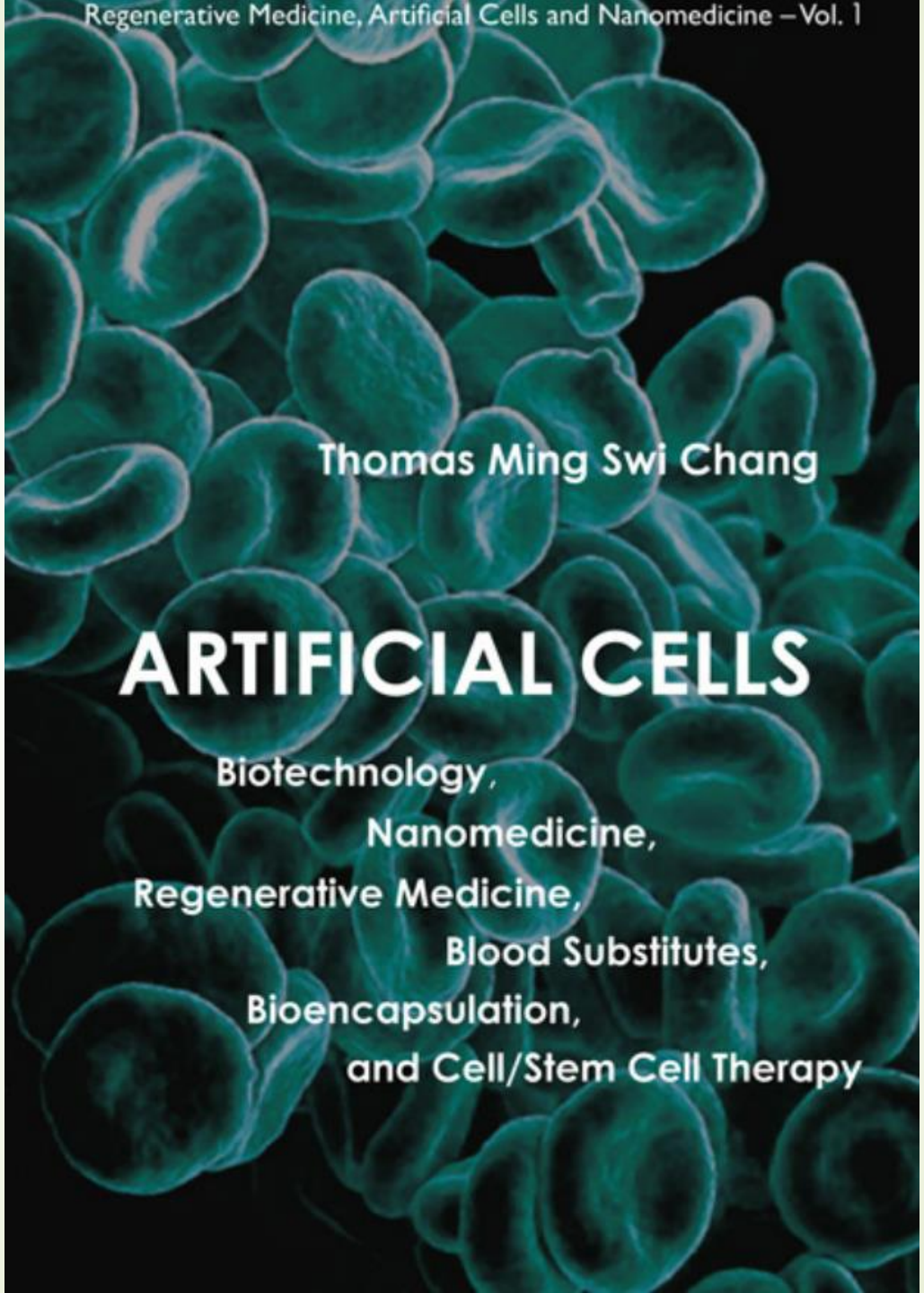


Fig. 14. Collman's "picket-fence" Fe(II)–porphyrin complex [Fe(TpivPP)(1-MeIm)] for reversible O_2-binding; H_2TpivPP is *meso*-tetra (α, α, α, α-*o*-pivalamidophenyl) porphyrin.

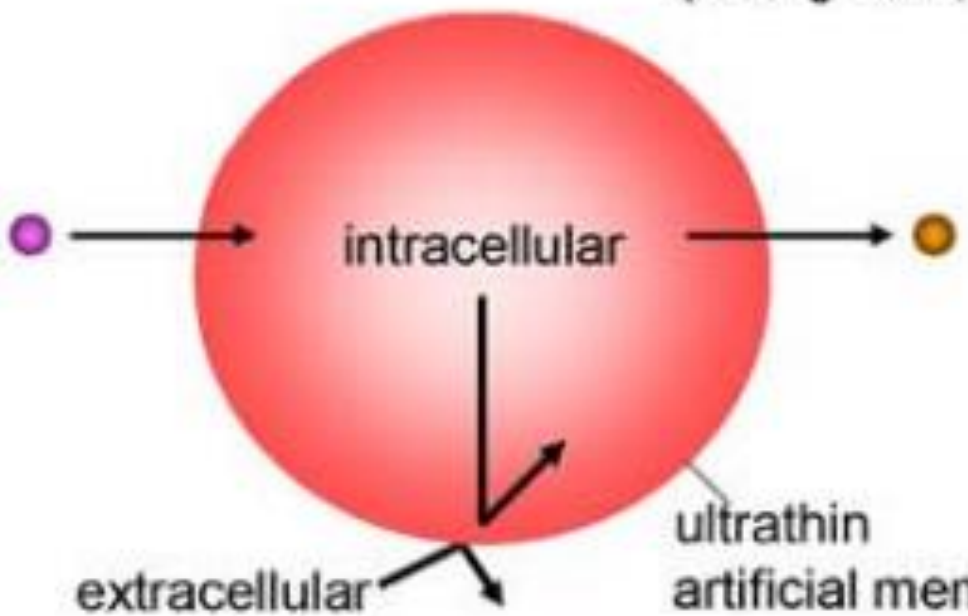

Regenerative Medicine, Artificial Cells and Nanomedicine – Vol. 1
Thomas Ming Swi Chang
ARTIFICIAL CELLS
Biotechnology,
Nanomedicine,
Regenerative Medicine,
Blood Substitutes,
Bioencapsulation,
and Cell/Stem Cell Therapy

What are Artificial Cells?

An artificial cell or minimal cell is an engineered particle that mimics one or many functions of a biological cell. The term does not refer to a specific physical entity, but rather to the idea that certain functions or structures of biological cells can be replaced or supplemented with a synthetic entity.

Basic Principles of early Artificial Cells

(Chang 1957,1964)



Like biological cells:

(1) content retained inside to
(2) act on permeant molecules
(3) release products
(4) intracellular environment
(5) extracellular environment

Artificial Cells (AC): Time Line of Ideas Since First Reported (1957)

1957 Chang	**First artificial cells prepared** with a synthetic membrane to replace RBC membrane and containing hemoglobin and red blood cell enzymes (emulsion phase separation, extrusion method or spray coating)
1964 Chang (*Science*)	Artificial cells (AC) containing enzymes, hemoglobin and cells formed by interfacial coacervation or interfacial polymerization to form membranes of polymer, crosslinked protein, polymer conjugated with protein, also crosslinked protein microspheres
1964, 1965 Chang	Nanobiotechnology: crosslinked protein (PolyHb) & conjugated Hb
1964,1965 Chang 1966: Chang *et al.*	Extrusion drop method for AC to encapsulate intact cells for immunoisolation in cell therapy
1965 Bangham *et al.*	Liquid crystal microspheres of multi-lamellar lipid (liposomes) as membrane model for basic research
1965, 1972a, 1973b Chang	AC for molecular sieve chromatography and separation
1965 Chang 1966 Chang *et al.*	AC with intracellular multi-compartments
1966 Chang	Silastic AC and microspheres containing protein
1966 Chang	AC containing magnetic materials and biological materials
1966, 1969a Chang	Ultrathin membrane AC containing adsorbents for hemoperfusion
1966 Clark & Gollan	Fluorocarbon as oxygen carrier
1967 Chang *et al.*	AC with polysaccharide complexed membrane for biocompatibility
1968 Chang & Poznansky (*Nature*)	Implanted enzyme AC for enzyme therapy in inborn error of metabolism (shown in congenital catalase-deficient acatalesemic mice)
1968 Bunn & Jandl	Intramolecularly crosslinked single Hb molecule
1968 Geyer *et al.*	Fluorocarbon effective in exchange transfusion in animal studies
1969d Chang 1972a Chang	AC with lipid-polymeric membrane or lipid-crosslinked protein membrane containing cyclic transport carrier (AC contains proteins)
1970–1975 Chang *et al.*	First clinical use of artificial cells in patients (in hemoperfusion)

1971a Chang (*Nature*)	Implanted enzyme AC for lymphosarcoma suppression in mice
1971b Chang	Nanobiotechnology: glutaraldehyde crosslinked Hb into PolyHb. Later, others used this method for blood substitutes in patients
1972a Chang	First monograph on *Artificial Cells*
1972b Chang (*Lancet*)	AC hemoperfusion resulted in Grade IV hepatic coma patient recovering consciousness
1973 Gregoriadis	First use of liposomes to entrap enzymes and drugs. Led to extensive development of liposomes as delivery systems
1975h Chang	Paper discussing one shot vaccine using AC
1976a Chang	Biodegradable polylactide microcapsules and microparticles containing proteins and hormones
1976 Tam, Blumenstein & Wong	Soluble dextran conjugated hemoglobin
1976 Bonhard *et al.*	Develop glutaraldehyde crosslinked PolyHb as blood substitute
1977–1985 Chang with Campbell, Cousineau, Ilan, Grunwald, Wahl, Yu etc.	Artificial cells containing multienzyme systems with co-factor recyclying for multistep enzyme reactions
1978 Naito & Yokoyama	Developed perfluorodecalin as blood substitute towards clinical trials
1980 Lim & Sun (*Science*)	Alginate-polylysine-alginate AC encapsulated cells
1980 Rosenthal & Chang	AC membrane of lipid-protein-polymer containing Na^+K^+-ATPase
1980 Djordjevich & Miller	Lipid membrane AC encapsulated hemoglobin
1985 Mitsuno, Ohyanagi	Clinical trials of perfluorodecalin as red blood cell substitute
1986 Yuan & Chang	AC containing microsomes and cytosol

1986 Sipehia, Bannard & Chang	AC membrane that exclude small hydrophilic molecules but permeable to large lipophilic molecules
1986 Chang, Bourget & Lister	Novel finding of extensive enterorecirculation of amino acids leading to the use of oral enzyme AC therapy to selectively remove specific unwanted systemic amino acid
1988 Tsuchida's group 2002 Tsuchida *et al.*	Development and *in vivo* testing of synthetic heme complex either to liposome or to recombinant albumin as blood substitute
1989a Chang, 1989 Palmour *et al.*, Chang	Clinical use of oral enzyme artificial cells in a patient (patient with inborn error of metabolism: Lesch-Nyhan disease)
1989 Moss *et al.*	Clinical trials with glutaraldehyde crosslinked PolyHb
1990 Hoffmann *et al.*	Recombinant human hemoglobin
1994 Yu & Chang	Biodegradable polymeric membrane nanoartificial red blood cells
1994 Soon-Shiong *et al.*	AC encapsulated islet transplantation in a type 1 diabetic patient. Insulin independence reported
1996 Prakash & Chang (*Nature Med*)	Oral artificial cells containing genetically engineered cells lower systemic urea in a uremic rat model
1996 Aebischer, Lysagth *et al.* (*Nature Med*)	Polymeric fiber encapsulation of genetically modified xenogeneic cells for intrathecal delivery of CNTF in amyotrophic lateral sclerosis patients
1998 D'Agnillo & Chang (*Nature Biotech*)	Nanobiotechnology of crosslinking of Hb, catalase and superoxide dismutase to form soluble nanodimension PolyHb-CAT-SOD
1998 Tsuchida	Lipid AC vesicle Hb: developed and tested in animal towards clinical use
1999 Philips *et al.*	PEG-lipid membrane AC containing Hb increases circulation time
2000 Liu & Chang	AC coencapsulating hepatocytes and adult stem cells
2001 Lörh *et al.* (*Lancet*)	Clinical trial of AC microencapsulated cell-mediated treatment of inoperable pancreatic carcinoma in patients
2002 Gould *et al.*	The life-sustaining capacity of human polyhemoglobin in trauma surgery clinical trials

2003 Chang, Powanda, Yu	PEG-PLA membrane nanodimension AC containing Hb and rbc enzymes
2004 Bloch *et al.*, Aebischer	Phase I clinical study for Huntington's Disease, using encapsulated cells engineered to secrete human ciliary neurotrophic factor
2004 Yu & Chang (*Melanoma Res J*)	Nanobiotechnological approach of PolyHb-tyrosinase: delays the growth of melanoma in a rat model
2006 Liu & Chang (*J Liver Trans*)	AC encapsulated bone marrow stem cells regenerate liver resulting in recovery and survival of rats with 90% of liver surgically removed

Present status of the basic features of artificial cells of macro, micron, nano and molecular dimensions

The general principles of artificial cells can form the basis of a large number of artificial systems. In addition to being of cellular dimensions in the micron range, they can also be in the macro range, nano range or molecular range. Furthermore, the membrane material includes polymer, biodegradable polymer, lipid, crosslinked protein, lipid-polymer complex, lipid-protein complex and membrane with transport carriers. Artificial cells can contain an unlimited variety of material individually or in combinations. These include cells, stem cells, enzymes, multienzyme systems, hemoglobin, magnetic materials, microorganisms, vaccines, genes for gene therapy, genetically engineered cells, adsorbents, drugs, hormones, peptides, proteins and others.

Uses of the AOC

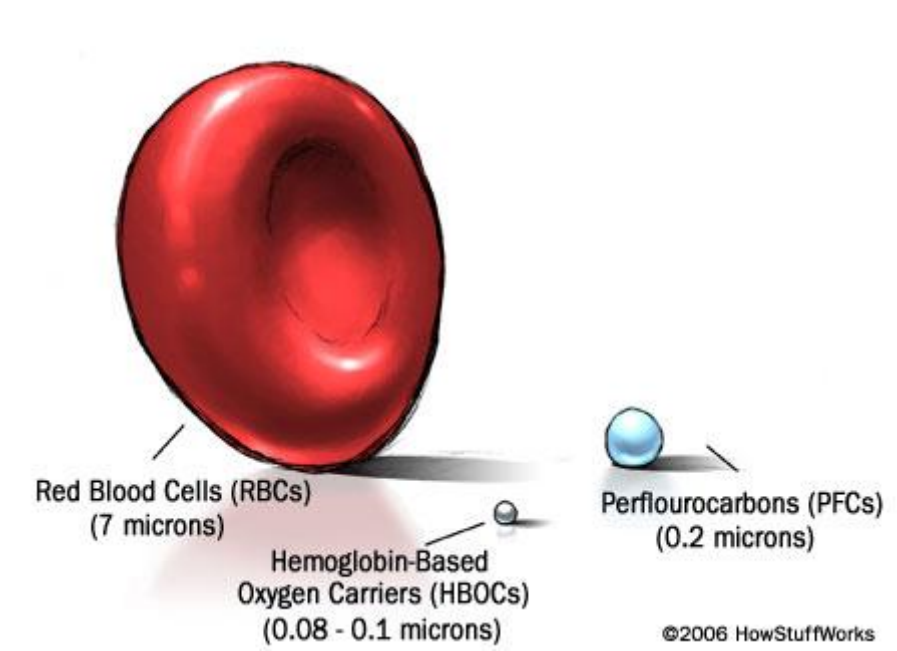
- Developed for 2 main purposes:
- Function as alternatives to blood transfusion (avoid, reduce, and delay transfusion of allogeneic blood)
- Improves the tissue oxygenators of organs with poor blood supply

- NOTE: It is a Red Blood Cell Substitute, not a complete replacement.
- The AOC is much smaller than a red blood cell, and can travel through smaller capillaries

Benefits and Disadvantages of the AOC

- Still going through intensive clinical trials, but plan to have/be:
- Long circulation half-life
- Long shelf life
- Oxygen delivered to the tissues in need
- Differing side effects (Flu-like symptoms or an increased risk in death/heart attack)
- Reasonable cost

Future of the AOC



- Pass the clinical trials
- Will be on the market
- Less of a health risk
- Health Care Coverage

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Artificial oxygen carriers: a new future?

Published online 2018 Feb 23

By Donat R. Spahn doi: 10.1186/s13054-018-1949-5

Despite the fact that allogeneic red blood cell (RBC) transfusions can be life-saving in exsanguinating trauma patients, many adverse events impacting patient outcome have documented. Therefore, artificial oxygen carriers were initially been developed as “blood substitutes” in the 1980s and 1990s. Artificial oxygen carriers can be grouped into haemoglobin-based oxygen carriers (HBOCs) and perfluorocarbon-based oxygen carriers (PFCs).

The clinical use of artificial oxygen carriers has mainly been studied in trauma and major surgery. HBOC studies in general did not show a benefit in the primary outcome parameter such as avoidance/reduction of RBC transfusions or 28-day mortality and signs of vasoconstriction/hypertension due to nitric oxide scavenging and increased relative risk of myocardial infarction and death were shown in a meta-analysis. Consequently, the Food and Drug Agency in 2008 put all HBOC trials on hold.

PFC studies in non-cardiac surgery were successful in reversing physiologic transfusion triggers and in reducing the need for allogeneic RBC transfusions. In addition, there were no major safety issues. However, a PFC study in cardiac surgery was prematurely stopped due to an increased incidence of neurologic adverse events, and this program has never been re-started.

In recent years, focus on the potential clinical use of artificial oxygen carriers moved away from “blood substitutes” towards “oxygen therapeutics”. Due to the relatively short half-life of 12–24 h, this may indeed be reasonable. However, clinical studies showing clear benefits in this new area are still scarce. The area with most documented evidence are “compassionate use” programs. In such programs, patients were treated with HBOCs at a median haemoglobin concentration of 39 g/l. Survival of patients with severe anaemia for whom RBC transfusion was not an option was clearly and significantly higher if treated with an HBOC. It is also conceivable that an HBOC may be capable of bridging a patient with severe anaemia until RBC transfusions become available.

In animal models, artificial oxygen carriers have also proven to be efficacious in relieving organ ischemia such as fetal hypoxia in pre-eclampsia and cerebral ischemia. However, in a recent study myocardial perfusion with an oxygenated HBOC-enriched solution did not reduce the infarct volume nor was post-ischemic cardiac function improved. In contrast, HBOC attenuated intense exercise-induced cardiac dysfunction.

Machine perfusion of liver grafts after prolonged cold ischemia with HBOC enriched perfusate appears to be efficacious in improving the condition of the liver graft prior to transplantation in multiple animal experiments. And recently the first human liver transplantation after machine perfusion with HBOC was performed. The use of artificial oxygen carriers in pre-transplant perfusion is also conceivable in other organs such as lung and heart. The future will tell whether HBOCs or PFCs are more efficacious.

PFCs may also be used as contrast agents and, in conjunction with magnetic resonance imaging, as infection tracers.

Finally yet importantly, artificial oxygen carriers look like a logical adjunct to Patient Blood Management. Patient Blood Management is already highly successful: a reduction in the use of allogeneic blood product transfusion of approximately 40%, a decrease in hospital mortality (−28%), infection rate (−21%), combined myocardial infarction and stroke (−31%), length of hospital stay (−15%), and annual costs ($7–29 million) has been described in a study on 605,000 patients in Western Australia. Nevertheless, having an artificial oxygen carrier to bridge the period of low haemoglobin/haematocrit or in the context of augmented haemodilution might broaden the spectrum of Patient Blood Management and may make it even more successful.

Artificial oxygen carriers thus may indeed have a new future in a large variety of clinical scenarios and diagnostic/therapeutic concepts.

Clinical Medicine Insights: Blood Disorders

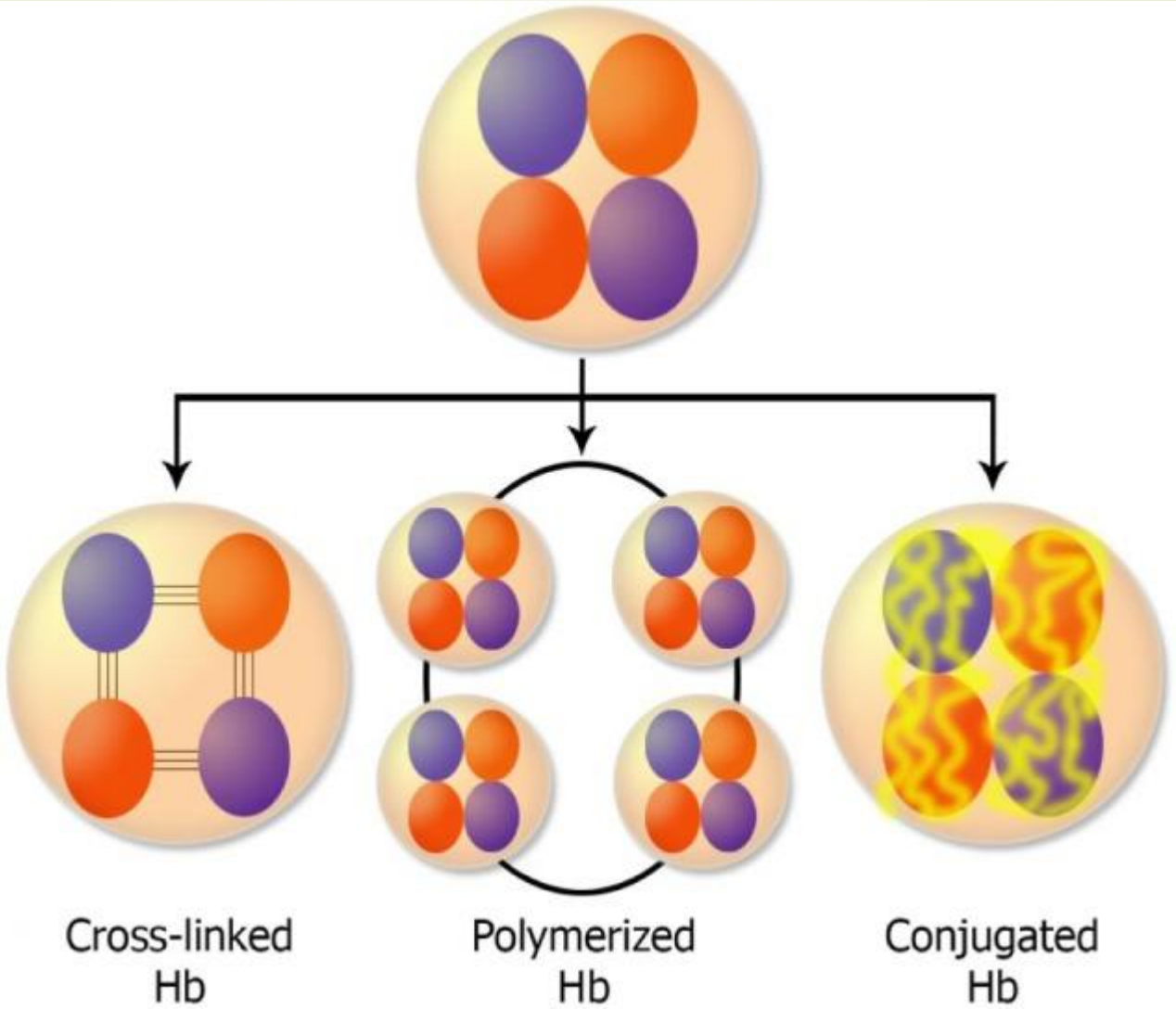
Artificial Blood Substitutes: First Steps on the Long Route to Clinical Utility

doi: 10.4137/CMBD.S38461

Published online 2016 Oct 27

Samira Moradi, Ali Jahanian-Najafabadi and Mehryar Habibi Roudkenar

The 21st century is challenging for human beings. Increased population growth, population aging, generation of new infectious agents, and natural disasters are some threatening factors for the current state of blood transfusion. However, it seems that science and technology not only could overcome these challenges but also would turn many human dreams to reality in this regard. Scientists believe that one of the future evolutionary innovations could be artificial blood substitutes that might pave the way to a new era in transfusion medicine. In this review, recent status and progresses in artificial blood substitutes, focusing on red blood cells substitutes, are summarized. In addition, steps taken toward the development of artificial blood technology and some of their promises and hurdles will be highlighted. However, it must be noted that artificial blood is still at the preliminary stages of development, and to fulfill this dream, ie, to routinely transfuse artificial blood into human vessels, we still have to strengthen our knowledge and be patient.



Three major classes of cellular HBOCs are polymerized, cross-linked, and conjugated Hbs. Spontaneous separation of Hb chains is prevented by various modifications. For example, in the cross-linked type, Hb chains are bound by intermolecular covalent bonds, in the polymerized type, they are bound by intermolecular covalent bond, and in the conjugated type, a polymer is bound to the surface of Hb.

Artificial cells: from basic science to applications

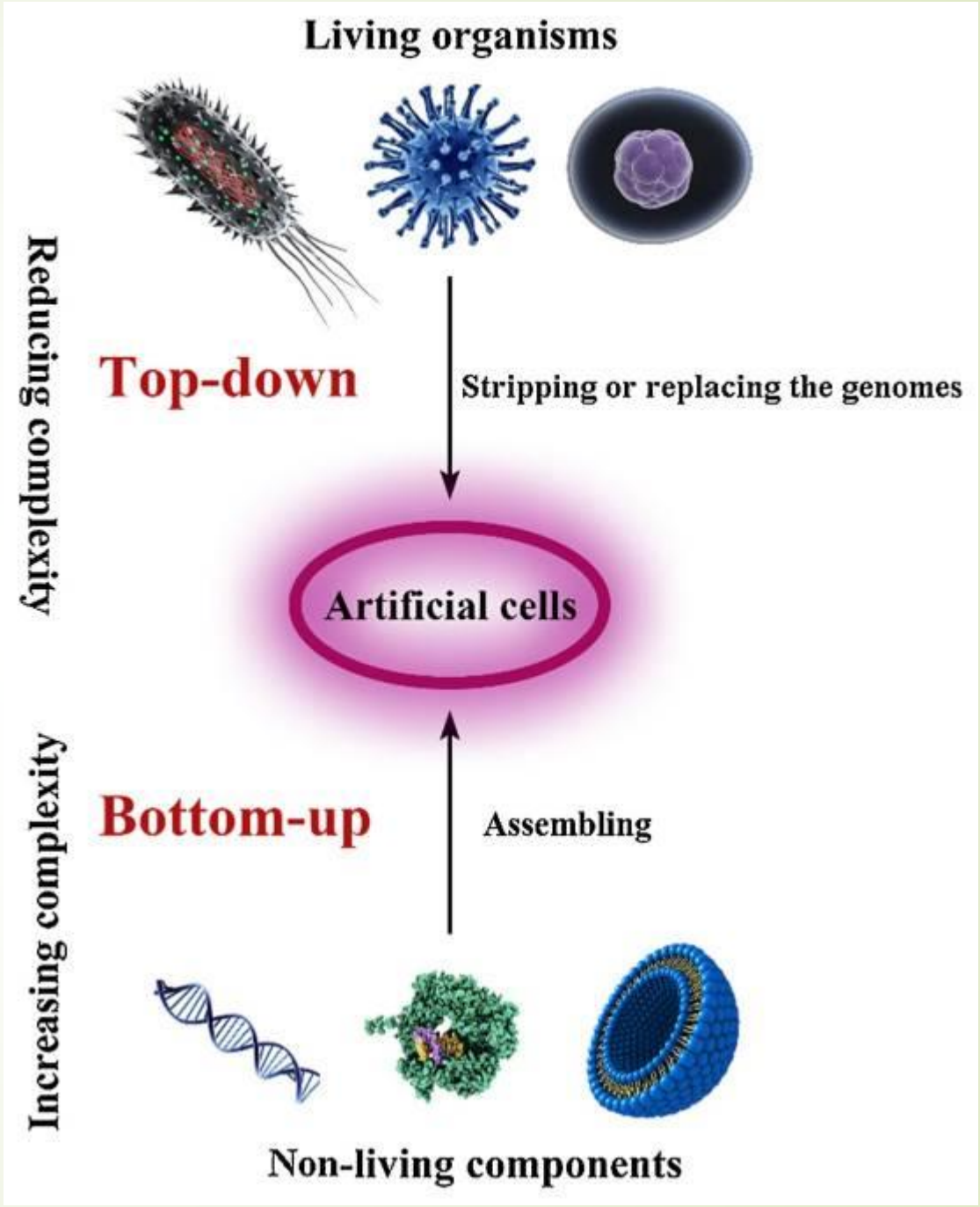
doi: 10.1016/j.mattod.2016.02.020

Can Xu, Shuo Hu and Xiaoyuan Chen

Published date: 2017 Jan 9

Artificial cells have attracted much attention as substitutes for natural cells. There are many different forms of artificial cells with many different definitions. They can be integral biological cell imitators with cell-like structures and exhibit some of the key characteristics of living cells. Alternatively, they can be engineered materials that only mimic some of the properties of cells, such as surface characteristics, shapes, morphology, or a few specific functions. These artificial cells can have applications in many fields from medicine to environment, and may be useful in constructing the theory of the origin of life. However, even the simplest unicellular organisms are extremely complex and synthesis of living artificial cells from inanimate components seems very daunting. Nevertheless, recent progress in the formulation of artificial cells ranging from simple protocells and synthetic cells to cell-mimic particles, suggests that the construction of living life is now not an unrealistic goal. This review aims to provide a comprehensive summary of the latest developments in the construction and application of artificial cells, as well as highlight the current problems, limitations, challenges and opportunities in this field.

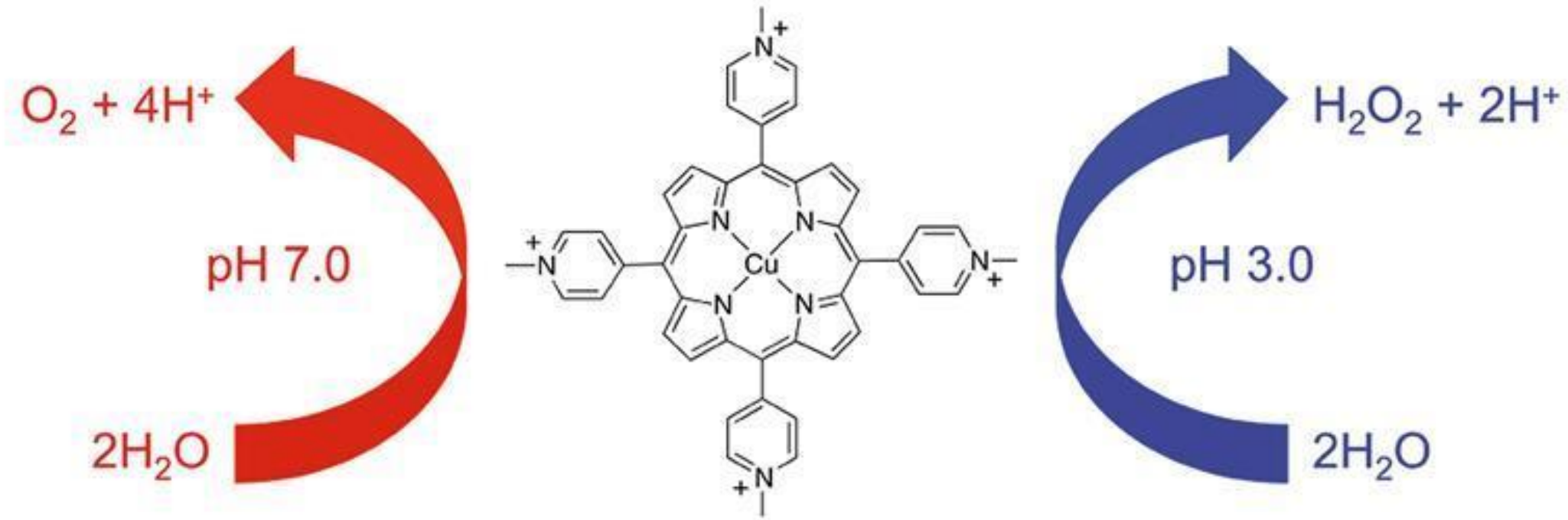
Approaches for the design and construction of artificial cells: In the top-down approach, artificial cells are created by stripping or replacing the genomes of living organisms (cells, bacteria or viruses), reducing their complexity, and only retaining minimum substances to maintain the essential life. In the bottom-up approach, artificial cells are constructed by assembling non-living components to form an integral that can replicate essential properties of natural cells.



Metal porphyrin complex takes significant step towards cheap water oxidation catalysts

A copper complex inspired by nature can efficiently split water at neutral pH, potentially opening the door to more commercially viable hydrogen fuel production. Hydrogen is an attractive alternative to oil and gas. The only product of hydrogen combustion other than energy is water, which is itself a source of hydrogen. Due to the energy required to split water into hydrogen and oxygen, a major research area centres on catalysts that can lower this barrier and make the reaction easier to perform. The most effective catalysts for this process contain noble metals such as ruthenium and iridium, both of which have drawbacks of high prices and scarcity. Now, a new study by a team of researchers led by Rui Cao, of Renmin University of China in Beijing, reports a copper porphyrin complex that can catalyse the water oxidation reaction at neutral pH, which is beneficial from an ease of use and safety standpoint, with an overpotential of 310mV. While this does not outperform conventional noble metal catalysts, it does represent a significant improvement in the performance of catalysts based on cheap and abundant elements. Previous copper catalysts have required much higher overpotentials and/or an alkaline pH.

Low overpotential water oxidation catalyzed by Cu^{II} porphyrin



The researchers were inspired by the role other metal porphyrins play in oxidising water during photosynthesis, where a magnesium porphyrin complex present in chlorophyll is a key component. ‘The other reason for using metal porphyrins for water oxidation catalysis comes from haem proteins, which contain iron porphyrin active site structures and play key roles in many oxygen-related biological processes. For example, cytochrome c oxidase and cytochrome P450 are the two most famous haem enzymes to catalyse oxygen activation in biology,’ says Cao.

With the porphyrin ligand conferring some much needed stability on the catalyst, the present demonstration of its water oxidation performance could make the field of metal porphyrin catalysis more attractive to researchers. ‘I’m actually a little surprised that it works as well as it does,’ comments Gary Brudvig, a water-splitting expert based at Yale University in the US. ‘We study porphyrins and we didn’t try to use copper porphyrins for water oxidation catalysis before, but now they’ve shown that it works, I think it’s an interesting system to explore.’

Cao’s team also discovered that this catalyst can produce hydrogen peroxide at acidic pH, a phenomenon rarely observed in this type of system, but one that could shed new light on the mechanism of the reaction. Edwin Constable, a water oxidation expert at the University of Basel in Switzerland, describes it as an unusual reaction. ‘If you understand what is happening with the hydrogen peroxide, you’re going to get a much better understanding of what is happening with the water oxidation system.’

New Insight into the Development of Oxygen Carrier Materials for Chemical Looping Systems

Zhuo Cheng, Lang Qin, Jonathan A. Fan and Liang-Shih Fan

https://doi.org/10.1016/j.eng.2018.05.002

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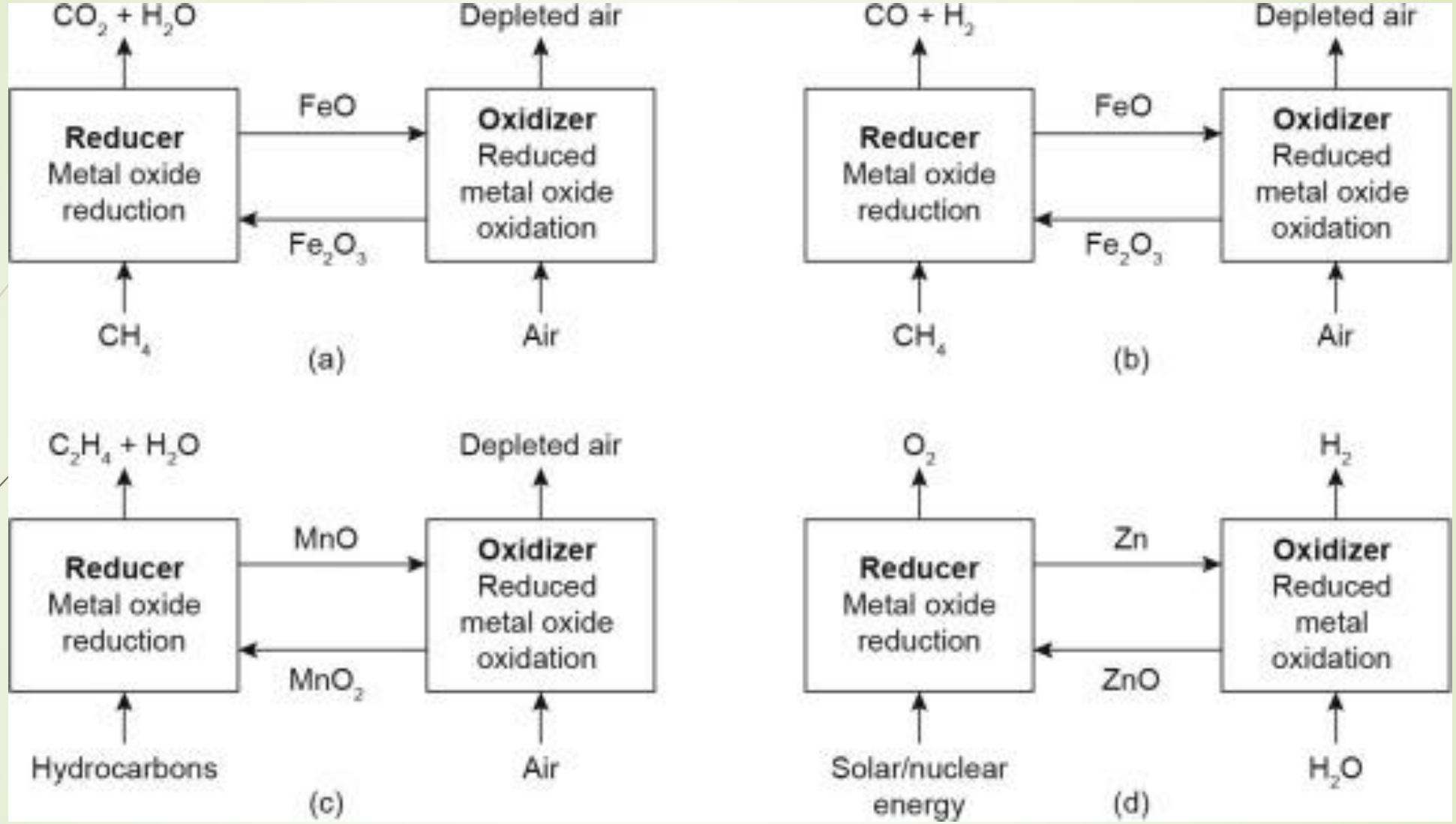
Chemical looping combustion (CLC) and chemical looping reforming (CLR) are innovative technologies for clea and efficient hydrocarbon conversion into power, fuels, and chemicals through cyclic redox reactions. Meta oxide materials play an essential role in the chemical looping redox processes. During reduction, the oxyge carriers donate the required amount of oxygen ions for hydrocarbon conversion and product synthesis. I the oxidation step, the depleted metal oxide oxygen carriers are replenished with molecular oxygen from the a while heat is released. In recent years, there have been significant advances in oxygen carrier materials fo various chemical looping applications. Among these metal oxide materials, iron-based oxygen carriers ar attractive due to their high oxygen-carrying capacity, cost benefits, and versatility in applications for chemica looping reactions. Their reactivity can also be enhanced via structural design and modification. This revie discusses recent advances in the development of oxygen carrier materials and the mechanisms of hydrocarbo conversion over these materials. These advances will facilitate the development of oxygen carrier materials fo more efficient chemical looping technology applications.



Classification of chemical looping systems. (a) Complete/full oxidation system; (b) partial oxidation system; (c) selective oxidation system; (d) solar/nuclear system

Chemical Science

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Low overpotential water oxidation at neutral pH catalyzed by a copper(II) porphyrin†

Check for updates

Cite this: DOI: 10.1039/c8sc04529a

All publication charges for this article have been paid for by the Royal Society of Chemistry

Yanju Liu,[a] Yongzhen Han,[a] Zongyao Zhang,[a] Wei Zhang,[b] Wenzhen Lai,[a] Yong Wang[cd] and Rui Cao*[ab]

Low overpotential water oxidation under mild conditions is required for new energy conversion technologies with potential application prospects. Extensive studies on molecular catalysis have been performed to gain fundamental knowledge for the rational designing of cheap, efficient and robust catalysts. We herein report a water-soluble CuII complex of tetrakis(4-N-methylpyridyl)porphyrin (1), which catalyzes the oxygen evolution reaction (OER) in neutral aqueous solutions with small overpotentials: the onset potential of the catalytic water oxidation wave measured at current density j ¼ 0.10 mA cm2 is 1.13 V versus a normal hydrogen electrode (NHE), which corresponds to an onset overpotential of 310 mV. Constant potential electrolysis of 1 at neutral pH and at 1.30 V versus NHE displayed a substantial and stable current for O_2 evolution with a faradaic efficiency of >93%. More importantly, in addition to the 4e water oxidation to O_2 at neutral pH, 1 can catalyze the 2e water oxidation to H_2O_2 in acidic solutions. The produced H_2O_2 is detected by rotating ring–disk electrode measurements and by the sodium iodide method after bulk electrolysis at pH 3.0. This work presents an efficient and robust Cu-based catalyst for water oxidation in both neutral and acidic solutions. The observation of H_2O_2 during water oxidation catalysis is rare and will provide new insights into the water oxidation mechanism.

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Artificial Blood Substitutes: First Steps on the Long Route to Clinical Utility

Samira Moradi, Ali Jahanian-Najafabadi, Mehryar Habibi Roudkenar

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Article information

Abstract

The 21st century is challenging for human beings. Increased population growth, population aging, generation of new infectious agents, and natural disasters are some threatening factors for the current state of blood transfusion. However, it seems that science and technology not only could overcome these challenges but also would turn many human dreams to reality in this regard. Scientists believe that one of the future evolutionary innovations could be artificial blood substitutes that might pave the way to a new era in transfusion medicine. In this review, recent status and progresses in artificial blood substitutes, focusing on red blood cells substitutes, are summarized. In addition, steps taken toward the development of artificial blood technology and some of their promises and hurdles will be highlighted. However, it must be noted that artificial blood is still at the preliminary stages of development, and to fulfill this dream, ie, to routinely transfuse artificial blood into human vessels, we still have to strengthen our knowledge and be patient.

Keywords

artificial blood, oxygen carrier, hemoglobin, red blood cells

Introduction

Being alive is impossible without blood, the complex liquid containing millions of chemicals and cells. When William Harvey for the first time described blood circulation, scientists started to think about a proper

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Detection of Hemoglobin-Based Oxygen Carriers in Human Serum for Doping Analysis: Confirmation by Size-Exclusion HPLC

Emmanuelle Varlet-Marie, Michael Ashenden, Françoise Lasne, Marie-Therese Sicart, Benedicte Marion, Jacques de Ceaurriz, Michel Audran

DOI: 10.1373/clinchem.2003.026591 Published March 2004

Abstract

Background: Hemoglobin-based oxygen carriers (HBOCs) are being developed as potential substitutes for the oxygen-carrying functions of erythrocytes, but athletes may obtain and experiment with HBOCs as an illicit means of enhancing oxygen transport. An electrophoretic technique has been developed to screen for the presence of HBOCs in blood samples (Lasne et al. *Clin Chem* 2004;50:410–5). Interest has focused on complementary methods that can provide legally defensible scientific evidence for the presence of HBOCs in blood samples collected for doping control.

Methods: The aim of this research was to develop a size-exclusion SEC-HPLC technique to identify in plasma or serum samples the presence of HBOCs that are currently under development. This method was also used to detect a polymerized bovine hemoglobin (Hemopure®) after infusion in 12 healthy males.

Results: The chromatograms of all HBOCs tested were clearly separated from the 54-min peak associated with human hemoglobin dimers. It was possible to differentiate between the different HBOC products based solely on their chromatographic profiles, provided they were at high concentrations. Differences were discernible not only based on the presence (or absence) of peaks, but also the separation between respective peaks. The profiles for serum samples collected from the men immediately after infusion of Hemopure showed a distinctive profile. The shape of the chromatographic profile remained consistent for at least 48 h.

Conclusions: Under the analytical conditions reported here, SEC-HPLC was able to separate native hemoglobin from the modified hemoglobin molecules present in each of the HBOC products studied. In tandem with electrophoretic screening, SEC-HPLC provides evidence of the presence of HBOCs and can therefore be regarded as a method that satisfies the criteria for use in an antidoping control setting.

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