Ferroquine: A Powerful Antimalarial and Promising Antitumor Therapeutic

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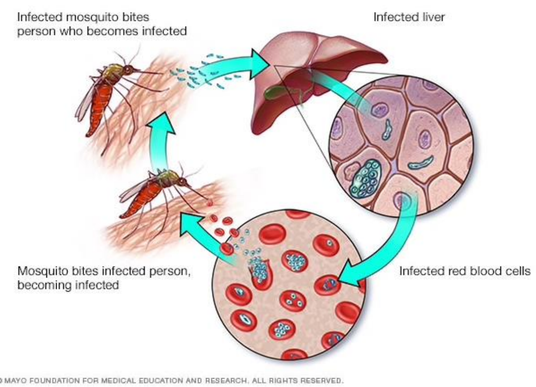
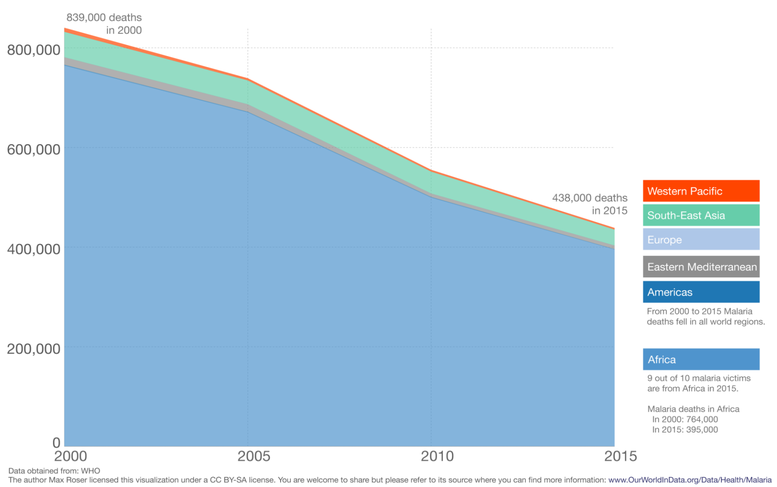
Abstract

To this day, cancer continues to be the world's second leading cause of death, making it gravely in need of innovative and successful therapies. Ferroquine, an antimalarial drug composed of a ferrocene derivative of Chloroquine, is one promising prospect. Currently undergoing clinical trials, the drug is seeking approval to be used as a cancer therapeutic. Ferroquine has been shown to possess strong abilities to impair prostate tumor growth in live test subjects. Thus, Ferroquine augments the anticancer activity for several chemotherapeutics demonstrating the possibility of Ferroquine being an adjuvant to current cancer therapy.. Ferroquine's superiority to chloroquine can be attributed to its organometallic properties due to the ferrocene core it has, as well as the strong internal hydrogen bond between the 4-amino group and the terminal nitrogen atom, which ultimately changes the molecules shape.

What is Malaria?



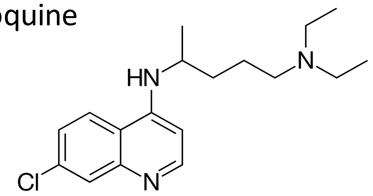
Global malaria deaths by world region, 2000 to 2015



Treatment

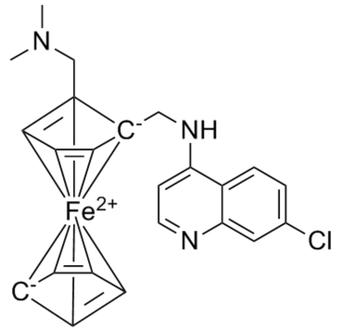
One of the most widely used antimalarials was known as Chloroquine (CQ). CQ enters blood cells and then the parasites cell's vacuole through simple diffusion and becomes protonated into CQ^{2+} due to the acidic environment. Unable to diffuse out due to its new charge, CQ ultimately binds to hematin and forms a complex toxic to the parasite.

Chloroquine

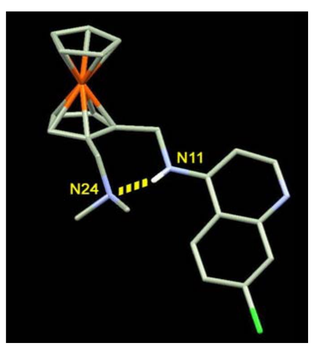


Increasing prevalence of parasites mutating and growing resistant to antimalarial drugs has made the development of new drugs crucial. Organometallic compounds have been synthesized to approach the elimination of parasites in a chemotherapeutic-like way; one being Ferroquine.

Ferroquine



Ferroquine proved to be a more powerful antimalarial than Chloroquine. Data showed FQ having a lower IC_{50} than CQ relative to hematin. The lower the IC_{50} value, the stronger the inhibitor. FQ showcased an IC_{50} of 0.8, as opposed to CQ with an IC_{50} value of 1.9.



Internal hydrogen bond between the 4-amino group and terminal nitrogen atom makes the molecule rigid. Such rigidity, along with increased lipophilic properties and weak basicity has been hypothesized to lead to more efficient membrane permeability.

Unique Redox Properties

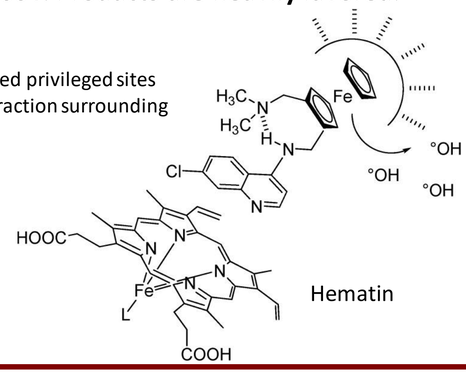
It has been showcased that FQ undergoes a unique redox reaction under the acidic and oxidizing environment in the vacuoles of the suspected parasitic cells. The result is hydroxyl radicals causing oxidative stress, and ultimately cell damage/death.

$$FQ(II) + H_2O_2 \rightarrow FQ(III) + HO^- + HO^\circ$$

Reversible one electron redox reaction yielding reactive oxygen species

Redox Potential for the Ferrocene/Ferrocenium ion is E°= +0.400V. Products are heavily favored.

Proposed privileged sites of interaction surrounding FQ.



Hematin

Cancer Applications

Cancer treatment testing was done by using cell lines that mimic the early progression of human prostate cancer were treated with FQ and induced about 60% cell death. *In vivo* experiments with mice showed inhibition of tumor growth. FQ is currently undergoing clinical trials with humans and the results look promising as it is the only chloroquine derivative to have made to the second phase of development.

References

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