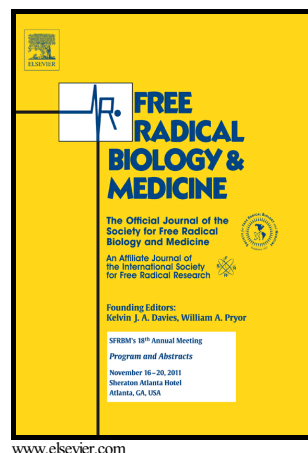


# Author's Accepted Manuscript

Targeting redox vulnerability of cancer cells by prooxidative intervention of a glutathione-activated Cu(II) pro-ionophore: hitting three birds with one stone

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PII: S0891-5849(18)31100-6  
DOI: <https://doi.org/10.1016/j.freeradbiomed.2018.06.021>  
Reference: FRB13817

To appear in: *Free Radical Biology and Medicine*

Received date: 19 March 2018  
Revised date: 1 June 2018  
Accepted date: 20 June 2018

Cite this article as: Xia-Zhen Bao, Fang Dai, Xin-Rong Li and Bo Zhou, Targeting redox vulnerability of cancer cells by prooxidative intervention of a glutathione-activated Cu(II) pro-ionophore: hitting three birds with one stone, *Free Radical Biology and Medicine*, <https://doi.org/10.1016/j.freeradbiomed.2018.06.021>

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**Targeting redox vulnerability of cancer cells by prooxidative intervention of a glutathione-activated Cu(II) pro-ionophore: hitting three birds with one stone**

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**ABSTRACT**

Altered redox homeostasis including higher levels of copper, the reduced glutathione (GSH) and reactive oxygen species (ROS) in cancer cells than in normal cells illustrates their redox vulnerability, and has opened a window for developing prooxidative anticancer agents (PAAs) to hit this status. However, how to design PAAs with high selectivity in killing cancer cells over normal cells remains a challenge. Herein we designed a 3-hydroxyflavone-inspired copper pro-ionophore (**PHF**) as a potent PAA based on the GSH-mediated conversion of 2,4-dinitrobenzenesulfonates to enols. Mechanistic investigation reveals that it is capable of exploiting increased levels of GSH in cancer cells to *in situ* release an active ionophore, 3-hydroxyflavone, inducing redox imbalance (copper accumulation, GSH depletion and ROS generation) and achieving highly selective killing of cancer cells upon specific transport of small amounts of Cu(II). To the best of our knowledge, it is the first example of Cu(II) pro-ionophore type of PAA which hits (changes) the

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