## Response to Reviewer 2:

***1.*** *This is a well written and very interesting overview of the potential impact of heme oxygenase inhibition (HO-1 and/or HO-2) in several diseases in which HO overexpression may be deleterious. The manuscript is clear enough and embellished with figures. I have only minor comments: About regulation of the HO activity (paragraph 2): a brief but more exhaustive description of the regulation of HO-1 transcription should be added including the roles of STAT3/IL-10/MAPK and NF-kB. Polymorphisms (SNPs) of HO-1 gene are briefly mentioned but nothing about the (GT)n repeat length polymorphism in the promoter region of the HO-1. Importantly, a long (GT)n repeat has been correlated with a lower transcription of HO-1 and higher inflammation and worse prognoses of several diseases. On the opposite, lower transcriptors of HO-1 have a stronger graft versus leukemia effect and have less disease relapse after allogeneic hepatopietic stem cell transplantation (ref: Kollgaard T, Kornblit B, Petersen et al. (GT)n Repeat Polymorphism in Heme Oxygenase-1 (HO-1) Correlates with Clinical Outcome after Myeloablative or Nonmyeloablative Allogeneic Hematopoietic Cell Transplantation. PLoS One. 2016;11(12):e0168210 or (perhaps less convincing) Yinghao Lu et al. Identification of heme oxygenase-1 as a novel predictor of hematopoietic stem cell transplantation outcomes in acute leukemia. Cell Physiol Biochem 2016;39:1495-1502. A recent relevant publication in the JCI insight showing the benefit to inhibit myeloid HO-1 in anti-tumor vaccination protocol might be added (JCI Insight: 2020 Jun 4;5(11):e133929. doi: 10.1172/jci.insight.133929. Heme oxygenase-1 orchestrates the immunosuppressive program of tumor-associated macrophages.*

**Answer:** As suggested by the Reviewer, we have added new references relative to the regulation of HO activity (Page 3; lines 71,72,75-79). In addition, articles suggested by the Reviewer were added and discussed (Page 3; 79-82, Page 8, Line 223, 224, 248-250).

***2.*** *About first generation of HO-1 inhibitors (paragraph 3.1) : authors describe the lack of selectivity but the given reference is related to HO-2 only. Moreover, HO-1 expression has been shown to be paradoxically induced by some HO inhibitors of the first generation. This could be mentioned.*

**Answer:** As suggested by the Reviewer, new references have been added and the contrary effect on HO-1 mRNA with some HO inhibitors was also discussed (Page 5; lines 139,140).

***3.*** *About cancer (paragraph 4.1, line 224) : References deal with in vitro tumor cell lines and it seems there is no reference with in vivo enhanced antitumor immunity weakening the conclusion.*

**Answer:** As suggested by the Reviewer, we have included references for *in vivo* and *ex vivo* studies relative to the antitumor activity mediated by HO inhibition (Page 9; lines 262, 263).

***4.*** *HO-1 in Alzheimer's disease is very complex. The authors state that HO-1 could lead to oxidative damages in Alzheimer's disease and that HO-1 inhibition attenuates oxidative damages and alzheimer's disease model in vivo. However, only one reference in the paper is mentioned and this should be strengthened by other references.*

**Answer:** As requested by the Reviewer, we have included more references about as to how over-expression of HO-1 may be detrimental during Alzheimer's disease and their impact on immune cells (Page 9; lines 289-294, Page 10, 296-304).

***5.*** *In the discussion: What is the meaning of MPP?*

**Answer:** As request by the Reviewer, we have changed MPP for metalloproteinase (Page 13, line 412).

We would like to thank the Reviewer the time and effort to review this work and hope that the current manuscript is acceptable for publication in International Journal of Molecular Sciences.