Reviewer’s report

Title: Identification of Oxidized Protein Hydrolase as a Potential Prodrug Target in Prostate Cancer

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Reviewer: Robert Getzenberg

Reviewer’s report:

This is a well written manuscript that describes the identification of oxidized protein hydrolase (OPH) as an esterase over-expressed in LNCaP cells. The concept of developing prodrugs that can be activated in a cancer specific fashion is an intriguing one that has been pursued by a number of approaches. In this work, the authors compare the protein expression of various prostate cancer cell lines in order to determine the differential expression of such esterases with the identification of OPH as a protein with this potential. While the concept being pursued is an important one and the protein chemistry demonstrating the differential expression of OPH is elegant, there are several important points that the authors should consider:

1. The data outlined in this manuscript do not really support the conclusions of the authors. What the authors have really shown here is that OPH is a protein that is differentially expressed in LNCaP cells but do not establish a correlation with tumorigenicity or aggressiveness. While the LNCaP cell line is more tumorigenic than the RWPE-1 cells, PC-3 and DU-145 cells are more tumorigenic in vivo. Based upon the data provided in the manuscript, the expression levels of OPH appear similar in the RWPE-1, PC-3 and DU-145 cells. In fact, if anything the levels are lower in the PC-3 and DU-145 cells than they are for the RWPE-1 line (Figure 7). This would argue against such a correlation. Furthermore, the authors do not examine the expression levels of OPH in human prostate cancer tissues. Therefore, the authors do not appear to be able to make significant interpretations regarding their findings and the tumorigenicity or aggressiveness of prostate cancer. This would appear to need to be corrected throughout the manuscript including the title, which does not appropriately reflect the studies outlined in the manuscript.

While this is an essentially important distinction, it does not take away from the value of the studies performed. With this in mind, the authors should refocus the manuscript to a distinction observed in LNCaP cells versus other prostate cancer cell lines. The findings noted here could be extended to human prostate cancer tissues of varying aggressiveness and perhaps correlate OPH expression with factors such as cancer specific survival utilizing retrospectively collected sample sets.

2. In the second paragraph of the Results, the authors make the statement that, “The staining intensity was greater for the LNCaP, DU-145 and PC-3 cell lysates compared to the RWPE-1 or RWPE-2 cell lysates”. This data does not appear
evident in the manuscript where only the expression in the LNCaP cell lysates appears to be significantly distinct.

3. The authors should better define how they normalize protein levels in their extracts. While equal quantities of protein are added to each well, a general stain or antibody should be utilized to make such a determination when comparisons are being made between cell lines as they are in this study.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.