Reviewer's report

Title: Differential expression of 12 histone deacetylase (HDAC) genes in gliomas: hypoexpression in glioblastomas

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Reviewer: Peter Atadja

Reviewer's report:

1. Is the question posed by the authors well defined? Yes
2. Are the methods appropriate and well described? Yes
3. Are the data sound? more needs to be done
4. Does the manuscript adhere to the relevant standards for reporting and data deposition? Yes
5. Are the discussion and conclusions well balanced and adequately supported by the data? No
6. Are limitations of the work clearly stated? No
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes
8. Do the title and abstract accurately convey what has been found? Not fully

The manuscript by Agda Karina Brodoloni Lucio-Eterovic et. al. sought to assess the global HDAC expression levels in glioblastomas, relative to their levels in normal brain tissue and low grade tumor tissues. They aimed to explore the relationship of HDAC levels in the context of the use of HDAC inhibitors in glioblastoma treatment. mRNA and protein assessments of HDAC isoform levels were done using real time quantitative PCR and western blotting respectively from micro-dissected tissues. Levels of histone acetylation were also assessed.

In general, the authors sought to explore an important question, as very little is known about the involvement of HDACs in brain tumorigenesis and how their expression levels might help to understand the effects of HDAC inhibitors. The authors duly noted that, some radiosensitization had been previously observed with HDAC inhibitors in glioblastoma cell lines. For their mRNA and protein analysis, the authors used the appropriate state-of-the-art techniques with sufficient number of tumor tissues to statistically determine significant differences in levels of expression. Overall, the data showed low levels of expression in class I HDACs and variable levels of expression of classes II and IV HDACs. Among the class II HDACs, HDAC 9 showed the highest expression levels in all tissues. A trend towards lower expression of class II HDACs was seen with higher grades of tumor. This trend reached statistical significance in some cases. Levels of acetyl histones H3 and H4 showed a strange reciprocal trend.

In light of the data obtained, the original question of relating levels of HDAC
isoforms to the use of HDAC inhibitors still remain unanswered. Especially, how
the data explain the known effect of HDAC inhibitors on tumor cell lines is not
clear. This has to be more thoroughly discussed instead of making a jump to
HATs which are not the focus of the study.

Additionally, to show that this trend of lower HDAC expression in higher tumor
grades has any biological significance, the authors must further determine
whether there are any correlative changes to known HDAC regulated genes with
increasing tumor grade.

Without doing additional studies to show that histone H3 decetylation is mainly
governed by class II HDACs in the brain, the authors cannot conclude that the
higher basal levels of histone H3 acetylation in glioblastoma is due to lower class
II HDAC expression. Furthermore, the authors have not explained the higher
levels of histone H4 in normal tissues and its absence in tumor tissue.

All the above concerns must be addressed and I am unable to recommend
publication at this time.