Reviewer’s report

Title: Pharmacological targeting of valosin containing protein (VCP) selectively kills canine lymphoma cells by inducing DNA damage

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Reviewer: Al Charest

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Comments to Authors:

The manuscript entitled “Pharmacological targeting of valosin containing protein (VCP) selectively kills canine lymphoma cells by inducing DNA damage” by Nadeau and colleagues describes the effects of inhibiting VCP in canine lymphoma cell lines. They first demonstrate that VCP is overexpressed in biopsy samples of high-grade canine lymphomas as compared normal lymph node or low grade lymphomas. They then show that in canine lymphoma cell lines that overexpress VCP, inhibition of VCP with an inhibitor (Eey1) result in a rapid apoptotic and cell cycle arrest response. They then further demonstrate that the apoptotic response is mediated by the formation of DNA breaks, which in turn activates p53 and the Cdkn2a locus. In general the manuscript is well written, the data is presented very clearly and the story flows well. There are however a few points that require the authors’ attention.

Major points:

- The authors need to address the dichotomy between the Eey1-induced apoptosis and the G1 arrest. Does the G1 arrest precede the apoptotic response or are these two phenotypes from separate pools of cells?

- PBMC treated with Eey1 are still affected, what is the mechanism by which these cells die? DNA damage (gH2AX) need to be done in PBMC treated with Eey1 in order to get to a mechanism.

- Finally, Eey1 activity through VCP need to be demonstrated by either knock down of VCP or use of Eey1 in a few non- or low-VCP expressing cell lines.

Minor points:

- quant of Fig 1C
- look into public database for relative expression of VCP in human cancers (eg. oncomine) and report results.
- Cdkn2a is a locus that codes for p16ink4a and p19arf (p14arf in human), authors need to better define what the PCR amplifies exactly or repeat the qPCR with probes for both p16ink4a and p19arf. This will shed light on the p53/MDM2/p19arf circuit.
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I have no competing interests