Reviewer's report

**Title:** Suberoylanilide hydroxamic acid, an inhibitor of histone deacetylase, suppresses vasculogetic mimicry and proliferation of highly aggressive pancreatic cancer PaTu8988 cells

**Version:** 1  
**Date:** 7 February 2014

**Reviewer:** Giovanni Tesoriere

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Title of the paper: Suberoylanilide hydroxamic acid, an inhibitor of histone deacetylase, suppresses vasculogetic mimicry and proliferation of highly aggressive pancreatic cancer PaTu8988 cells by Xingdong Xu et al.

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The authors show that SAHA, a histone deacetylase inhibitor, inhibits pancreatic cancer cell survival and vasculogetic mimicry. In particular SAHA induces G2/M arrest, cyclin B1 degradation, p21/p27 upregulation and finally Sema-4D down-regulation associated with AKT inhibition.

In my opinion the study of the effects exerted by SAHA on pancreatic cancer cells is very interesting. However some important aspects have not been focused with accuracy by the authors. In particular it is not clear the mechanism through which SAHA caused the death of pancreatic cancer cells.

In the discussion the authors report that “one key signaling pathway that is frequently over-activated in pancreatic cancer is AKT/mTOR, which is responsible for cancer cell survival, proliferation, migration and metastasis”. In addition the authors report in the results that SAHA (10 and 20 µM) significantly inhibited activation of AKT. These considerations strongly suggest that survival and proliferation of pancreatic cancer cells is under the control of the over-activated AKT/mTOR pathway while SAHA inhibited this pathway and consequently survival and proliferation of pancreatic cancer cells.

In order to demonstrate this thesis it is necessary to ascertain the effect of SAHA on:

- the level of mTOR, the level of phospho-p70S6 kinase, which is an important substrate of mTOR,
- the level of ULK1 which controls activation of autophagy. (Major compulsory revisions)

The results could allow to clarify the modalities through which SAHA is capable of inhibiting the survival of pancreatic cancer cells.

**Level of interest:** An article of outstanding merit and interest in its field
**Quality of written English:** Acceptable

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