Reviewer's report

Title: Targeting Notch signaling for the treatment of pediatric soft tissue sarcomas

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Reviewer: Heinrich Kovar

Reviewer's report:

Rosella Rota et al. provide a comprehensive review of the most recent literature on the role of NOTCH receptor signaling and downstream pathways for the pathogenesis of pediatric soft tissue sarcomas, synovial sarcoma, Ewing sarcoma and rhabdomyosarcoma. They very nicely put the molecular findings in context with developmental aspects, clinical findings, and clinical drug development issues. At the end of each chapter, they come up with questions and hypotheses that may help to steer future research into the subject. Even though some of these hypotheses may be considered quite speculative since they are based on the mere integration of independent studies and results rather than on direct experimental evidence (such as NOTCH involvement in synovial sarcoma, for which direct evidence is completely missing), they are intriguing and worthwhile to be tested. That is why this review is interesting to read.

Minor essential revisions:

i) Even though direct evidence for NOTCH involvement in synovial sarcoma is missing, a recently closed NCI sponsored phase I/II study at MSCC (NCT01154452) of a hedgehog inhibitor combined with a gamma secretase inhibitor (RO4929097) included adult patients with advanced synovial sarcoma. It would be nice if the authors mentioned that in their review (text and/or Table 2).

ii) On page 11, second paragraph, the authors refer to a paper by Schaefer et al. with "In a recent report, Schaefer et al. showed that, in a global gene expression profile on 27 primary samples of ES, the Notch signaling is among the most represented de-regulated pathways besides to be over-represented in metastatic tumors [41]". It is true that this paper says so in the text, but the Table to which Schaefer et al. refer does not support this statement, instead it lists the Hedgehog pathway. Since it is not clear where the mistake occurred, in the Table or the text, I would recommend omit reference to this paper in the context of NOTCH in Ewing sarcoma. The same is true for Table 1, in which the authors refer to reference 41 by NOTCH signaling to be “overexpressed in primary tumors”. Even if Schaefer et al. meant that genes of the NOTCH signaling pathway were over-represented in a comparison between localized and metastatic tumors, it does not necessarily mean that they were overexpressed but differentially expressed.

iii) In Table 1: The contents of the paper referred to in Reference 1 is consistent with an oncosuppressor and not a Pro-tumor activity of NOTCH in Ewing
sarcoma


v) Figures 2 and 3 are common text book knowledge and almost every NOTCH review presents very similar figures. Since no new aspect is added to these figures they should be omitted.

vi) Several grammatical errors and a few typos make substantial proofreading by a native English speaker necessary.

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**

I declare that I have no competing interests