Reviewer's report

Title: Parallel Screening of FDA-Approved Antineoplastic Drugs for Identifying Sensitizers of TRAIL-Induced Apoptosis in Cancer Cells

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Reviewer: Ladislav Andera

Reviewers report:

The manuscript submitted by Taylor et al. named “Parallel Screening of FDA-Approved Antineoplastic Drugs for Identifying Sensitizers of TRAIL-Induced Apoptosis in Cancer Cells” describes combinatory analysis of a pro-apoptotic effects of group FDA-approved anti-cancer drugs from the Johns Hopkins Chemical Compound Library (JHCCL) and the recombinant TRAIL on selected prostate and pancreatic cancer-derived cell lines. As a major screening tool was selected TRAIL-resistant variant of the prostate carcinoma cell line PC3. This MTT-based screening revealed in addition to already known drugs sensitizing cancer cells to the recombinant TRAIL as doxorubicin or mithramycin also another DNA-damaging drug mitoxantrone as a potent enhancer of TRAIL-induced apoptosis of tested prostate or pancreatic carcinoma cell lines. However, besides this finding, which was not in addition assisted by any mechanistic analysis of this sensitization (though the authors claim to work on it), the data in the manuscript just using only one methodical approach only in a comprehensive way present already known facts. Thus the novelty of the manuscript is rather scarce and therefore I do not recommend it to be accepted in this version.

My comments and suggestions:

a/ Major Compulsory Revisions:
- There are missing controls with normal pancreatic or prostate human epithelial cells or with human hepatocytes (e.g. at the combinatory LD50).
- Only MTT assay was used for the analysis of cell proliferation; additional cell proliferation (e.g. CellTiter Blue, x-Celligence or clonogenic assay) should be used at least in selected experimental setup; also apoptosis array as Annexin V-FITC/PI would be helpful.

b/ Minor Essential Revisions:
- It might be worthy to titrate TRAIL at fixed e.g. LD50 concentration of the sensitizing agent – 10 ng/ml is relatively low concentration and thus some effects with less enhancing drugs might be missed.
- Also in addition to cancer cells pre-treatment with the sensitizing drugs it would be interesting to analyze an effect of co-treatment/co-application.

c/ Discretionary Revisions:
- Pg. 8 - 20% of less proliferating (presumably apoptotic) PC3-TR cells is not a
negligible susceptibility – it would be if sensitivity to TRAIL at 1 #g/ml drops below 5%.
- Why PC3 and PC3TR so differ in their sensitivity to sole doxorubicine and mithramycin?

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.