Reviewer's report

Title: Increased expression of Transcription Factor TFAP2 alpha correlates with chemosensitivity in advanced bladder cancer

Version: 1 Date: 22 November 2010

Reviewer: Alexandre Zlotta

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The authors found that high levels of nuclear and cytoplasmic TFAP2alpha were predictors of increased overall and PFS in BC patients treated with cisP based therapy. TFAP2alpha silencing increased Cis and Gem sensitivity.

siRNA directed knock down of TFAP2alpha stimulated SW780 cell line proliferation whereas in p53 mutated T24 it did not affect proliferation.

TFPA2alpha induces p21 dependent transcriptional activation.

General comment

Studies improving our understanding of CisP responsiveness or absence of response to chemo in BC patients are utterly needed and therefore the authors should be commended for trying to bring an additional piece of information.

1. There was no association between TMA staining and overall and PFS when applying the analysis to the entire cohort of patients whereas it did reach stat significance in patients with lymph node invasion.

Although the authors refer to 2 previously described multicenter adjuvant chemotherapy trials using 2 different chemo regimens, it does not appear very clearly how many patients had node positive disease, what the extent of the lymph node dissection was. A table summarizing the data, even if these have been previously described would help the manuscript to be more reader-friendly.

1. The kappa for TFAP2 alpha between researchers is far from breathtaking (0.75 and 0.68). Any comment about any applicability of this marker in future studies

2. Several series have outlined the benefit of adjuvant chemotherapy even in the absence of lymph node positivity. Was there any trend regarding the predictive value of TFAP2 alpha in T3 BC where one would anticipate a subset of patients to harbor micro-metastatic disease and therefore potentially benefit from adjuvant chemo if their cells are responsive.

3. It would make sense to think of a study using neoadjuvant chemotherapy and TFAP2 alpha. Do the authors have access to any of these patients. Linking complete or partial response to TPAP2 alpha expression would greatly enhance our understanding of this marker and support the concept.

4. Was there any reason as the authors had access to TMAs not to stain for p53,
p21 and other related markers?
The authors have described in detail their hypothesis regarding p53 dependent
p21 activation and how they explained differences in chemosensitivity whether
they used T24 or SW 780 cells but why not looking directly at p53
overexpression together with p21 and maybe BAX and Ki-67 in the bladder
tumors themselves? Or using a functional assay for p53?

5. The authors state that TPFAP2 alpha silencing augmented gemCis sensitivity
and did not stimulate proliferation in the p53 mutated and non tumorigenic cell
line, corresponding to clinical findings in lymph node negative patients. However,
a percentage of patients with lymph node negative actually harbor node positive
disease and a subset of BC non metastatic to the nodes is clearly TP53 mutated
but tumorigenic...
The authors conducted functional chemosensitivity studies but did not
reintroduce TFAP2 into a TFAP2 negative bladder cancer cell line to add
robustness to their findings although data had been shown in colon cancer cell
lines.

Minor comments

1. A couple of typos should be corrected throughout the manuscript and in the
legends of the figures: for instance Fig 5 axis is labelled as ralativ expression. It
should read relative.

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

**Quality of written English:** Acceptable

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