Reviewer’s report

Title: Molecular determinants of context-dependent progesterone receptor action in breast cancer

Version: 1 Date: 14 November 2013

Reviewer: Anne Gompel

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major compulsory revisions

The topic of the review is very interesting and the group of C. Lange is one of the leader on the subject of PR and had recently focused on the role of PR phosphorylations in the signal transduction and breast cancer. The field is still quite unexplored and will beneficite from the contribution of this group.

Despite a real interest of this review there are several points which might be modified before its full acceptation:

1) The introduction is too Manichean as well as some statement made later in the text; stating that progesterone is the primary mitogen in the breast is misleading: at puberty and thereafter as known from all the physiology, it is absolutely clear that estrogens are the main contributors to the breast development in the human species as well as in others mammalian species. Progesterone will have absolutely no effect on a breast not primed by estradiol!

Progesterone has not been proven to be a mitogen on normal luminal human breast cells. Several papers (early from the group of RB. Clarke and more recently from A. Gompel) showed that in normal human breast tissues implanted in the mice, only estradiol displayed a proliferative effect and progesterone did not display any additional proliferative activity.

There is also a lack of specificity when using the terms of stem cells presented here to be target of P whereas this has been mostly demonstrated in the mice and in the human it is rather progenitor luminal cells which are the potential targets of its regulation from the rank/l pathways. There are also evidence for a role for estradiol on the “stem cells”.

2) In addition, breast cancers which are ER+ and PR+ have a much better prognosis than ER+ PR- and hormone receptor negative or triple negative cancers. Can the authors remind that and modulate their statement about “aggressive phenotype”.

3) Concerning HRT, it must be recalled that progesterone and dydrogesterone might be associated with different risk of breast cancer than synthetic progestins (see papers from F. Clavel Chapelon et al and Lytyinen et al).

4) When addressing the different impact of MPA only the androgen effect is reported. Please add the glucocorticoid potency of this progestin and the potential consequences on breast cancer as recently published.
5) The “liver toxicity of antiprogestin” concerned onapristone but is not applicable to others steroidal SPRMs such as mifepristone, ulipristal acetate etc. please correct in the first citation.

6) Still a lot of work is needed to define which impact will have to better figured the various phosphorylated PR forms. Most of the clinical trials with antiprogestins have been so far disappointing in breast cancer, maybe because the right subset of breast cancers was not well selected. However and as addressed by the authors, antiestrogens/aromatase inhibitors are quite efficient in most of luminal A breast cancers. It is not clear in which putative categories antiprogestins could be indicated. Can the authors describe which subset of patients should be candidate for these treatments?

7) It would be useful to get a drawing for the phosphorylation sites of PR and their consequences on the PR biological functions if possible.

8) Please correct in figure 1 BR-B in PR-B

Quality of written English: Acceptable

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

Declaration of competing interests:

research grant form HRA-Pharma Ulispristal acetate on normal breast occasional consultancy for pfizer on CEE/Basedoxifen