Reviewer's report

Title: Heat shock protein90 in lobular neoplasia of the breast

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Reviewer: David Ross Sibson

Reviewer's report:

(Major revision 1)
The main focus of this manuscript appears to be the expression of heat shock protein (Hsp) in association with estrogen receptors alpha and beta in Lobular Neoplasia (LN) of the breast. The introduction provides a useful background to the role of Hsps, Hsp90 in particular and the significance of the latter for advanced cancer, prognosis and as a therapeutic target. This serves as justification to determine Hsp90 levels in LN as the results could have implications for the relative risk associated with these borderline lesions and suggest opportunities for chemo-prevention. This could have been brought out more fully and I therefore suggest a major compulsory revision to set out more fully the context of the study. In conjunction with similar efforts with regard to the results and discussion this will provide an opportunity to improve the impact of the findings which currently are presented in a relatively neutral fashion. In presenting Hsp90 for example more mechanistic details are available and could be included. Reference 6 is emphatic that Hsp90 levels are increased in cancer yet the introduction simply states that it’s expression is abnormal. Being definitive with a fuller description would allow the significance of the low levels of Hsp90 seen in the LN as reported in the results to be better presented and appreciated.

(Major revision 2)
The spectrum of atypical lesions found in breast is and likely will continue be the subject of much review, discussion and debate. The second sentence in the third paragraph of the introduction is therefore questionable and the reference 13 alone is not adequate or a direct reference. The consensus WHO classification of 2002 and references therein for example would be better or at least included as a (first) addition. Similarly, a more detailed introduction to the estrogen receptor positivity in the lesions of interest would be beneficial, especially given that they are part of the subject matter for the study. Although the majority are positive for estrogen receptor alpha for example this is not necessarily exclusively the case and comments to this effect would be desirable.

(Major revision 3)
Finally, Hsp90 interacts with a variety of proteins so more should be made of why the hormone receptors in particular have been singled out. Perhaps for example with some discussion of the receptors themselves and their positivity / or negativity as appropriate. What are they considered to do ? This would help again in establishing the significance of the findings reported in the results
section.

Additional sample, example references that may be helpful are provided below:


P. Workman, F. Burrows, L. Neckers, And N. Rosen
Drugging the Cancer Chaperone HSP90: Combinatorial Therapeutic Exploitation of Oncogene Addiction and Tumor Stress

Silencing of HSP90 Cochaperone AHA1 Expression Decreases Client Protein Activation and Increases Cellular Sensitivity to the HSP90 Inhibitor 17-Allylamino-17-Demethoxygeldanamycin
Joanna L. Holmes, Swee Y. Sharp, Steve Hobbs, and Paul Workman

The methods are appropriate. A key and valuable feature of the materials is the use of LN from presumed cancer free individuals. This has limited the number of cases on which the conclusions are based.

(Minor essential revision 1).
Antibodies for ER beta have been controversial, a note of justification for choice would be helpful

(Major revision 4)
Based on the information I received and there was nothing in the manuscript to suggest I should expect more it is impossible to comment on the results. Only 2 immuno-histochemistry images are provided and these concern the detection of Hsp90. It is appreciated that the ER data may have been reported elsewhere but it should be included here to provide context. Only statistical measures are provided and there is no data tabled to allow either the statistics to be checked or the overall nature of the data to be evaluated. It is impossible to know for example how much heterogeneity was observed for example in association of ER alpha or beta with Hsp90. What are the proportion of ER alpha negative/ ER beta negatives, alpha positives / beta negatives, alpha negatives / beta positives, alpha / beta positives and to what extent were the alternatives associated with the Hsp90 measures? ER beta can be difficult to detect. Has any attempt been made to subclassify the lesions and if so what sized groups are obtained and are there any new associations that are possible as a result? A major revision is required to give a fuller description of the results.
Note the current data limitations above. Accepting the statistical significance it is left to rationalise the reported low levels of Hsp90. This would be simply explained if the LN studied are benign lesions containing cells not yet subject to the stresses occurring in invasive cancer and thus a stress response has not been triggered. That the levels are lower than even normal breast could be a systematic variable brought about by the nature of the cells characteristic of the lesions. Given that classifications have not been reported in the manuscript more is needed.

Para 2 discussion. Whilst Hsp90 is essential to the function of ER alpha and beta it is not obvious that these proteins alone should actually be associated with Hsp90. More discussion and justification is needed in this regard.

Technical limitations in terms of possible lack of reproducibility are acknowledged in the manuscript. Comments concerning the ease of detection of the estrogen receptor beta in particular would be welcomed. Given that classifications have not been reported in the manuscript more is needed.

In the main the authors adequately refer to their earlier work and that of others. See exceptions above. A fuller description of their earlier work regarding the estrogen receptors in their target lesions should be considered.

The title is limited but probably appropriate.

The manuscript is clearly written.

It is not currently possible to assess the statistics.

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.

Declaration of competing interests:

I declare that I have no competing interests