Reviewer's report

Title: Activation of the steroid and xenobiotic receptor, SXR, induces apoptosis in breast cancer cells.

Version: 2 Date: 23 September 2008

Reviewer: Ratna K Vadlamudi

Reviewer's report:

This is an interesting manuscript that tests the hypothesis that orphan receptor SXR may play a role in the induction of apoptosis in the breast cancer cells. The rationale for this study is sound. Using proliferation and cell cycle assays, authors provided strong evidence that SXR signaling play a key role in the growth inhibitor action of various compounds that function as activators of SXR in estrogen receptor (ER) positive breast cancer cells. Using mechanistic studies, they have provided evidence that SXR mediated induction of iNOS levels, local production of NO and up regulation of p53 as the mechanism by which SXR signaling contributes to growth inhibition. Even through the manuscript is little bit descriptive, it contains some clinically useful information and these findings have clinical implications in potential combinatorial therapy for breast cancer cells. Addressing the following concerns will further strengthen the manuscript.

1. Even through the manuscript uses estrogen receptor (ER) positive cells, the role of ER in SXR pathway is not addressed. Is SXR mediated inhibition is only limited to ER positive cells. Is ER needed for SXR mediated induction of iNOS. Do the observed effects hold good in ER negative, p53 WT positive cells.

2. Figure 3 C, 3D: the quality of the figure is not good. The numeric values of p53/GAPDH ratios do not correlate very well with the intensity of the bands shown in the figures.

3. Figure 4F: The data using 1400 W is little bit confusing and contradictory and the explanation given on page 18 does not clearly explain the effects seen in lane 3 and lane 6. If 1400W is an activator of SXR transcription, then why it is inhibiting RIF mediated induction of P53 in lane 6 is not clear.

4. Figure 5C; It would be better if authors show the expression of SXR as effected by control SCR or SXR specific siRNA in one gel rather than as two separate pieces attached together. in addition use of single siRNA for down regulating SXR and p53 is a concern

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.