Reviewer's report

Title: Antiprogestin mifepristone inhibits the growth of cancer cells of reproductive and non-reproductive origin regardless of progesterone receptor expression

Version: 2 **Date:** 20 February 2011

Reviewer: Georg Sager

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Antiprogestin mifepristone (MF) inhibits the growth of cancer cells of reproductive and non-reproductive origin regardless of progesterone receptor expression

by

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Major Compulsory Revisions

1) There are none or few path-breaking observations in this study. The authors continue along the same track. They have extended the observation of a “non-genomic” effect of mifepristone to 10 cell lines wherein only MCF-7 possessed nPRs. They also repeat their observations of G1-cell cycle retardation effectuated by Cdk2.

2) In the introduction and discussion they have not cited papers which are highly relevant, especially Fjelldal et al. MCF-7 Cell Apoptosis and Cell Cycle arrest - Non-genomic Effects of Progesterone and Mifepristone (RU-486) Anticancer Research Vole 30, pp, 4835-4840 (2010) comparing the PR-positive cell line MCF-7 and the PR-negative cell line C4-I. Also the two previous papers (Moe et al 2009a, 2009b) demonstrated the non-genomic effect of progesterone (PG) and MF in the PR-positive endometrial cell line Ishikawa.

3) It is of concern that the authors do not distinguish between growth and the “tumor bulk”, i.e. the cell densities being a function of both input (proliferation) and output (apoptosis and necrosis). It has been known in about two decades that PG causes a G1-arrest, and that most but not all report that MF retards the cell cycle with a G1-arrest. However, both the PG and MF are very effective inducers of apoptosis. This mechanism is probably more important in reducing cell densities than the cell cycle retardation. For the supraphysiological concentrations of PG and the high concentrations of MF, in the interval between 1 -100 µM, both act as agonists which reinforce the others’ actions. This has not been discussed. The nPR will be saturated 4-10 times above Kd, which means concentrations of 25 – 50 nM for both PG and MF. In the discussion which is far too long, the mPR, a GPCR, has not been mentioned. The mPR has recently been reviewed by Thomas 2007 (Endocrinology 148, 705-718) and their following papers have supplied us by intriguing knowledge.

4) In pharmacological studies variable DTs are usually not corrected for, and it is difficult to understand the rationale for this. The response (Ex) for each concentration (X) tested is related to Emax. The IC50-value is calculated from the fractional response. In cell studies it is important to determine the time-dependent development of effect. An apparent change in sensitivity may occur from day 1 to day 10, for example, but that is another issue than variable DTs.

5) A weakness of the hypothesis is that the MF-concentrations are not specified. The methods are sound and adequately described, but the rationale for the DT-corrections is not well argued for. In the results figure 2, 3 and 5 should be omitted and the results described in the text. As mentioned above Discussion should be substantially shortened.

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