Reviewer's report

Title: Suppression of Homologous Recombination by insulin-like growth factor-1 inhibition sensitizes cancer cells to PARP inhibitors.

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Reviewer: Haim Werner

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This manuscript by Amin et al deals with the correlation between homologous recombination (HR) and sensitivity to IGF1R inhibition. The hypothesis postulated by the authors is that IGF1R inhibition might sensitize HR proficient cancers to PARP inhibitors. This hypothesis is based on previous findings showing that: (1) impairment of HR is found in approx 50% of ovarian and breast cancers; and (2) tumors with BRCA1 mutations express high levels of IGF1R mRNA and protein.

The authors employed ovarian and breast cancer cells with known BRCA1 status, and evaluated HR functionality by RAD51 foci formation assays. The expression of proteins involved in the IGF1R pathway was assessed by Western blots. The impact of IGF1R tyrosine kinase inhibitor on RAD51 mRNA and protein expression was also measured. Finally, the combined effect of IGF1R and PARP inhibitors was addressed by clonogenic assays.

The authors report that cells with mutated or methylated BRCA1 exhibit impaired HR function and display over activation of IGF1R signaling components. These cells are more sensitive to IGF1R inhibition compared to HR proficient cells. In addition, the IGF1R inhibitor reduced RAD51 mRNA and protein expression in HR proficient cells. This is a very interesting, well-thought paper. Furthermore, the manuscript is clinically relevant given the disappointing results obtained so far with IGF1R inhibitors in cancer patients and, additionally, the need to better identify patients who might benefit from this biological therapy.

A number of points need to be addressed by the authors:

Discretionary revisions:

Lines 95-98: Figure 5 is presented before Figures 3 and 4. Please, number figures in the order they are discussed in the text.

Lines 154-157: The authors state “The data … supports an interaction between the two pathways, as demonstrated by the enhanced protein levels of IGF1R, pIGF1R, pAKT and pS6 …”. The authors need to soften this statement as changes in these proteins were not always seen in the paper.

Minor essential revisions:

Lines 103-105: The authors state “we observed the over-expression of IGF1R
and its downstream pathway proteins in patient derived tumor cells with absent BRCA1 expression, as shown in Fig. 5A. This is a very general statement which needs to be formulated in a much more careful and informative manner. While clear differences are seen in pIGF1R levels, it is difficult to see differences in total IGF1R, pS6, and pIRS-1. The authors need to expand on the analysis of each particular protein.

Lines 107-109: The authors state “Cells with low or absent BRCA1 expression, and with a concurrent HR deficiency, were more sensitive to IGF1Rki as compared to HR proficient cells (Fig. 4A, B).” Again, this is a very general and non-informative statement. Please expand: What was the difference in sensitivity? Dose-response analysis? Statistics?

Lines 129-131: The authors state “Phosphorylated proteins of the IGF1R pathway (pIGF1R, pIRS-1, pS6) was also determined …”. Again, as indicated above, this is a general and non-informative statement. Results must be described in more detail. In addition, it should be “were” also determined (not “was”).

Lines 145-146: Please, expand. It is important to describe the Results obtained.

Line 185: Should be “we have shown”.

Figure 2E, title, should be “Breast cancer cells”

Reference 46 is incomplete.

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

**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