**Reviewer's report**

**Title:** Glibenclamide inhibits cell growth by inducing G0/G1 arrest in the human breast cancer cell line MDA-MB-231.

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**Reviewer:** JYOTI NAUTIYAL

**Reviewer's report:**

Ms: Glibenclamide inhibits cell growth by inducing G0/G1 arrest in the human breast cancer cell line MDA-MB-231.

By: Mariel Nunez et al.

The primary objective of the current manuscript by Nunez et al is to examine mechanisms of human breast cancer cells MDA-MB-231 growth inhibition induced by glibenclamide. The results show that Gli has cytostatic effect induced by G1 arrest of the cells. Gli does not induce cell death or differentiation and it required continuously for its cytotoxic effects on MDA-MB 231 cells.

Comments: The research subject is quite groundbreaking as it attempts to exploit potassium channel inhibitors in treatment of triple negative breast cancers. Studies of this kind will prove to be pioneering work in associating the potassium channels to understand cancer pathology and development effective therapeutic for cancers. This is an interesting report on a subject that is of clinical significance. The manuscript is well written and the conclusion is supported by the experimental data.

However, there are few concerns which need to be addressed to improve the manuscript.

1) The authors did not provide a good rationale for using potassium channel blockers for conducting this study in hormone independent human breast cancer cells MDA-MB-231 cells. The very first experiment and result of this study does not fit in the manuscript. There are several publications that demonstrate resistance of hormone independent breast cancer cells, including MDA-MB-231 to growth inhibition by tamoxifen (Park et al, 2012). If the intent is to show that Gli alone is as effective as tamoxifen, then the cell mode is not appropriate. Conversely, the authors need to use some other agent that is effective growth inhibitory agent in these triple-negative breast cancer cells. This experiment and result does not gel well in the manuscript.

2) The therapeutic use of glibenaclamide for human breast cancer is not imminent from this work. The dose utilized to study the cytostatic effects is quite high (IC50= 25µm). Additionally, the cytostatic effects are reversible and Gli need to be continuously present to show its effects. For an aggressive cancer like triple negative breast cancer, this may not be the best therapeutic. There are studies that utilize various agents to sensitize the hormone independent cells to tamoxifen (Giacinti et al 2012). Since the first results shows that Gli effects were
similar to the combined treatment, the possibility of using Gli as combined therapy is also ruled out.

3) Statement regarding effects of gli or potassium channel blocker need to be checked and corrected for conflicts terms. Do these agents favor/ inhibit hyperpolarization or depolarization? There are conflicting statements in background and discussion sections.

More studies are required to demonstrate therapeutic benefit of Gli and there is need to explore other combination therapies with Gli. In its current state, the manuscript needs some revision to rationalize the experiments and discuss the observations in light of developing a potential therapy for the notoriously aggressive triple-negative breast cancers.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

NONE