Reviewer's report

**Title:** Calcitriol restores antiestrogen responsiveness in estrogen receptor negative breast cancer cells: A potential new therapeutic approach

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**Reviewer:** Antimo Migliaccio

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The paper by Santos Martinez et al. shows that calcitriol induces expression of ER# in ER- breast cancer cells, thereby restoring the hormone-sensitive phenotype and anti-estrogen responsiveness. The experiments presented in the paper show that upon calcitriol treatment anti-estrogens down regulate cell growth of ER negative cancer cells and CCND1 and EAG1 potassium channel expression. This action is mediated by the Vitamin D receptor (VDR), as it is abolished by a VDR antagonist. This suggests a potential use of Vitamin D in the treatment of the hormone resistant breast cancer.

This is a potentially very interesting report as it address the question of the rescue of hormone-responsiveness of hormone independent cancers, which are characterized by a poor prognosis and reduced disease-free survival. The experiments shown in this paper undoubtedly demonstrate that calcitriol restores, at least partially, the hormone-dependence of ER- cells, but say very little about the mechanism by which this occurs.

The main pitfall of this paper is the lack of mechanistic insight of the findings. Therefore I think that:

1- A study of ER promoter to identify sites for VDR could greatly improve the paper impact.

2- As the Authors hypothesize that the up regulation of ER# by calcitriol is probably mediated by MAPK, a MAPK assay, as well as analysis of other proteins possibly involved in the MAPK pathway (e.g...Src, Ras ,Mek) to investigate whether their activity is related to calcitriol action

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

' declare that I have no competing interests