Abstract #5338

Pamiparib as a non-P-glycoprotein substrate PARP inhibitor can overcome *ABCB1*-mediated multidrug resistance in ovarian cancer cells

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Background

- Ovarian cancer is commonly treated with debulking surgery followed by platinum-taxane based chemotherapy and targeted therapy (PARP inhibitors).
- However, a key challenge facing these therapies is drug resistance caused by various mechanisms, one of which is the P-glycoprotein (P-gp, encoded by the *ABCB1* gene) mediated multidrug resistance. Tumor cells with high P-gp protein expression extrude P-gp substrate drugs from intracellular space and reduce drug efficacy.
- Since Paclitaxel and some PARP inhibitors such as Olaparib are P-gp substrates, their clinical benefit may be compromised in primary or acquired P-gp positive patients. Pamiparib, on the other hand, is PARP inhibitor that is not P-gp substrate, therefore, it is reasonable to hypothesize that Pamiparib will have better efficacy in P-gp high ovarian tumors.

Pamiparib shows similar *in vitro* sensitivity with Olaparib in P-gp negative cells

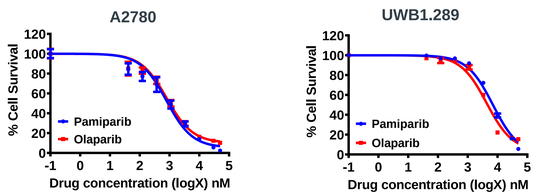


Figure 1. P-gp non-expressing ovarian cancer cell lines A2780 and UWB1.289 are equally sensitive to Pamiparib and Olaparib. Two P-gp negative ovarian cancer cell lines are cultured in the presence of Pamiparib or Olaparib and monitored for cell growth.

Cell lines developed acquired resistance to Olaparib or Paclitaxel up-regulates P-gp protein

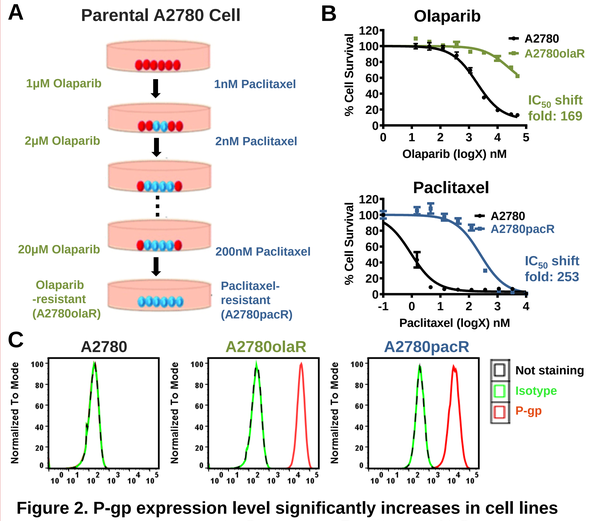


Figure 2. P-gp expression level significantly increases in cell lines with acquired resistance to Olaparib or Paclitaxel. (A) Olaparib or Paclitaxel acquired resistant cell lines are developed through prolonged *in vitro* culture of sensitive A2780 cells with stepwise increased concentrations of individual drug. A2780, parental cells; A2780olaR, Olaparib resistant cells; A2780pacR, Paclitaxel resistant cells. (B) Parental A2780 and resistant cell lines are cultured with indicated drugs and monitored for cell growth. (C) Olaparib and Paclitaxel resistance leads to increased expression of P-gp protein.

P-gp inhibitor Verapamil largely reverses the resistance to Olaparib and Paclitaxel

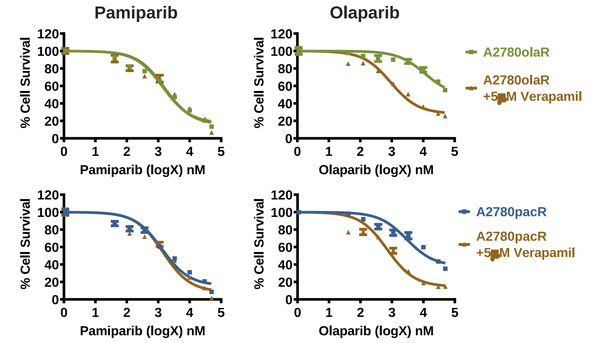
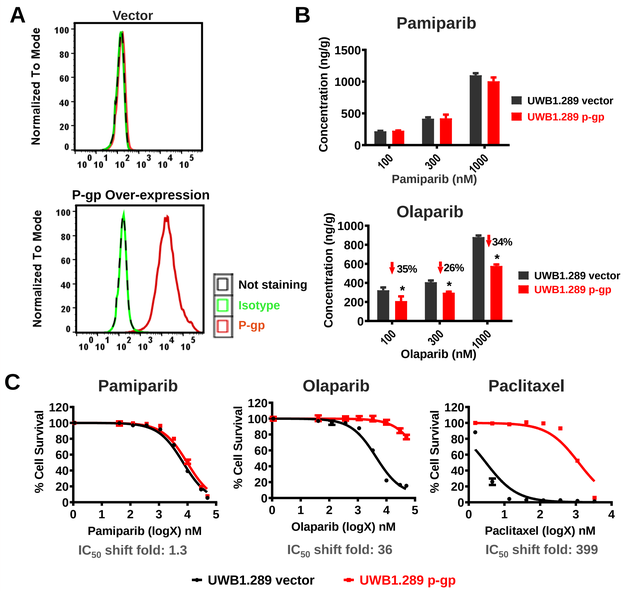


Figure 4. Sensitivity to Olaparib or Paclitaxel in A2780-derived resistant cells can be largely restored by P-gp inhibitor Verapamil. Verapamil is P-gp high affinity substrate and has been shown to bind and inhibit P-gp functions. Addition of Verapamil into cell culture significantly sensitizes resistant cells to Olaparib or Paclitaxel induced death. Pamiparib sensitivity, however, is not affected by Verapamil.

Pamiparib sensitivity is not affected by P-gp over-expression



Olaparib-resistant or Paclitaxel-resistant A2780 cells are sensitive to Pamiparib

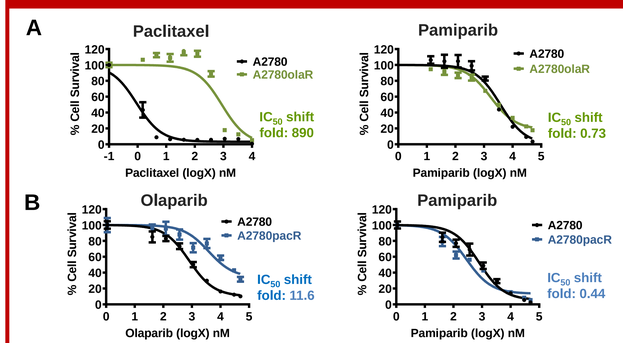


Figure 3. Olaparib-resistant or Paclitaxel-resistant A2780 cells are sensitive to Pamiparib. (A) A2780olaR cells are cross-resistant to Paclitaxel but still sensitive to Pamiparib. (B) A2780pacR cells are cross-resistant to Olaparib but not Pamiparib. (C-D) Intracellular concentration of Pamiparib is similar between parental A2780 and resistant cells, while lower intracellular Olaparib is observed in both A2780olaR (C) and A2780pacR (D) cells.

Figure 5. P-gp over-expression causes UWB1.289 cells resistant to Olaparib and Paclitaxel but not Pamiparib. (A) P-gp is over-expressed in UWB1.289 cells and protein level has been confirmed by FACS. (B) Cellular concentration of Pamiparib is not affected by p-gp over-expression, while that of Olaparib decreases in p-gp over-expressing cells. (C) P-gp over-expression leads to resistance to Olaparib and paclitaxel but not Pamiparib.

Pamiparib overcomes P-gp mediated resistance to Olaparib and Paclitaxel in CDX model

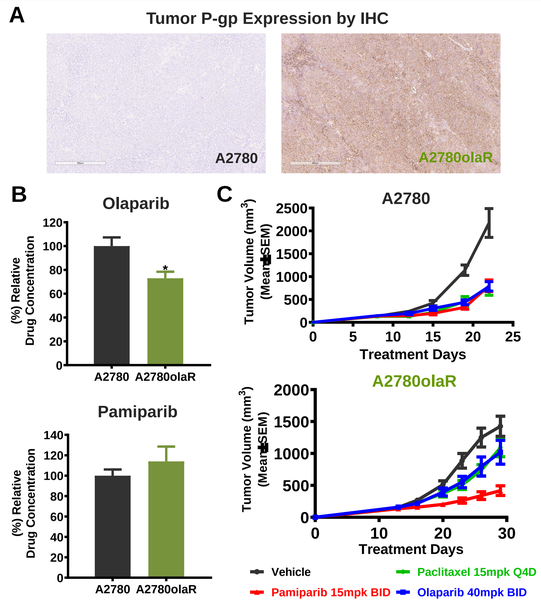


Figure 6. Pamiparib is efficacious in A2780olaR CDX model, which is resistant to both Olaparib and Paclitaxel. (A) High P-gp level in A2780olaR tumor and negative expression in A2780 sample have been confirmed by IHC. (B) Intra-tumor concentration of Olaparib decreases in P-gp positive A2780olaR model compared to P-gp negative parental A2780. Pamiparib intra-tumor concentration is equivalent in both models. (C) Olaparib, Pamiparib and Paclitaxel each demonstrates significant tumor growth inhibition in A2780 model. On the contrary, only Pamiparib remains efficacious in A2780olaR model, while efficacy of Olaparib or Paclitaxel is dramatically compromised.

Conclusion

The results highly suggest that Pamiparib as a non-P-gp substrate PARP inhibitor can overcome ABCB1-mediated drug resistance in tumors and may provide additional clinical benefits to ovarian cancer patients.