Establishment of PARPi Resistant CDX Platform

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Introduction

The development of PARP inhibitors (PARPi) has revolutionized cancer treatment, particularly for BRCA1/2 deficient tumors. However, the emergence of PARPi resistance poses a significant challenge. Our study aimed to explore the mechanisms of this resistance, focusing on the role of DNA end resection.

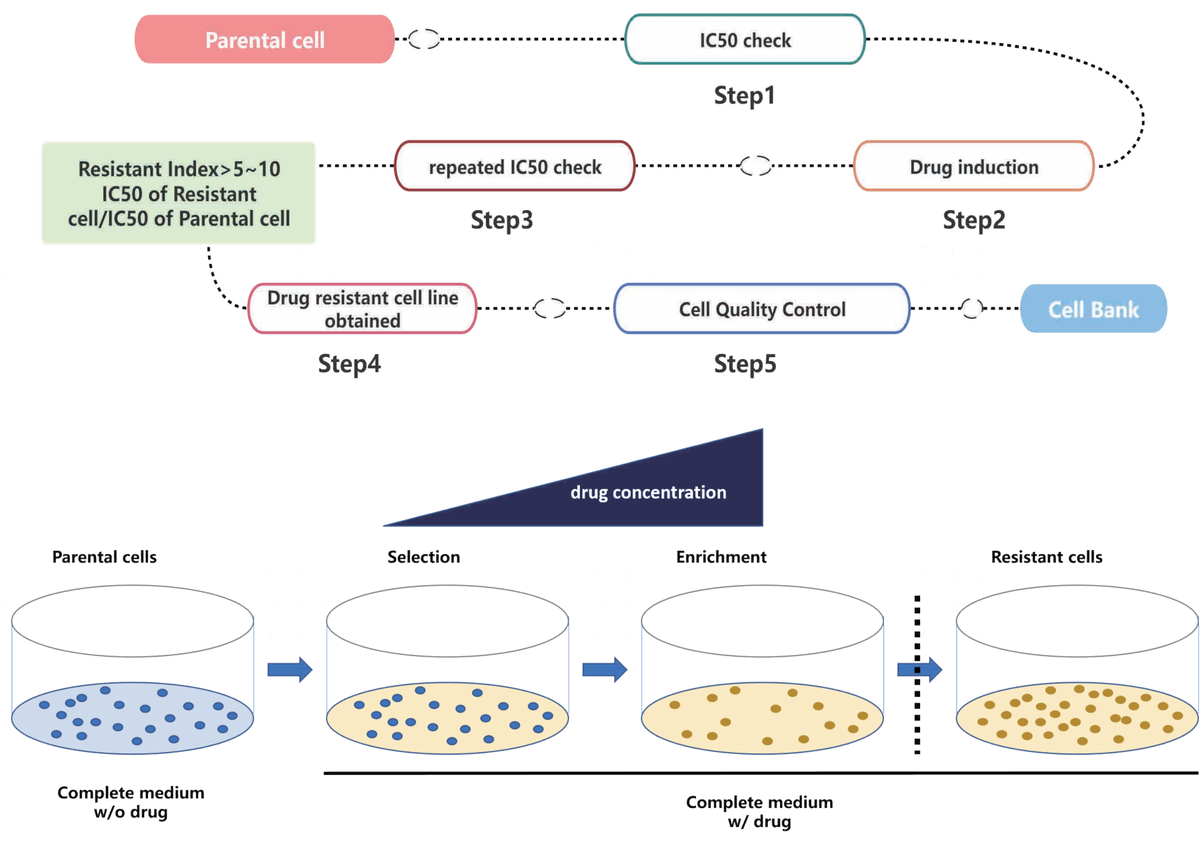
We induced resistance in the MDA-MB-468 cell line using Talazoparib and Olaparib, creating in vivo models to evaluate drug sensitivity. RNA-seq analysis identified significant gene expression changes in resistant cells, hinting at altered signaling pathways.

Our results showed increased resistance indices and poor drug response in resistant cell lines, confirming resistance development. Establishing over 40 drug-resistant cell lines, our platform is poised to facilitate the advancement of PARP-targeted therapies, offering insights into overcoming PARPi resistance in cancer treatment.

Method

In vitro drug. inducing → Detection of resistanceindex → Iranscriptome sequencing → Drug resistance CDX model

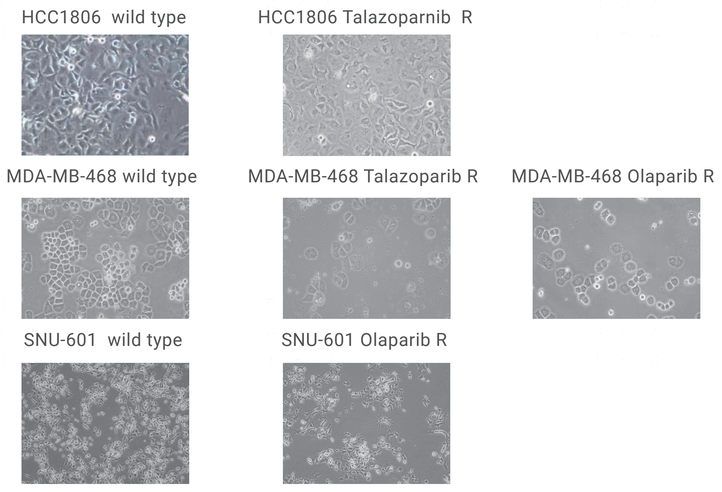
1. Schematic diagram of establishment of drug-resistant cell line



Drug-resistant cell lines were generated by incubation with conditioned medium contained escalated drugs concentration for 4-6 months which mimic the process of drugs resistance tumors during the clinical chemotherapy.

Results

1. Quality control of cell morphology and doubling time



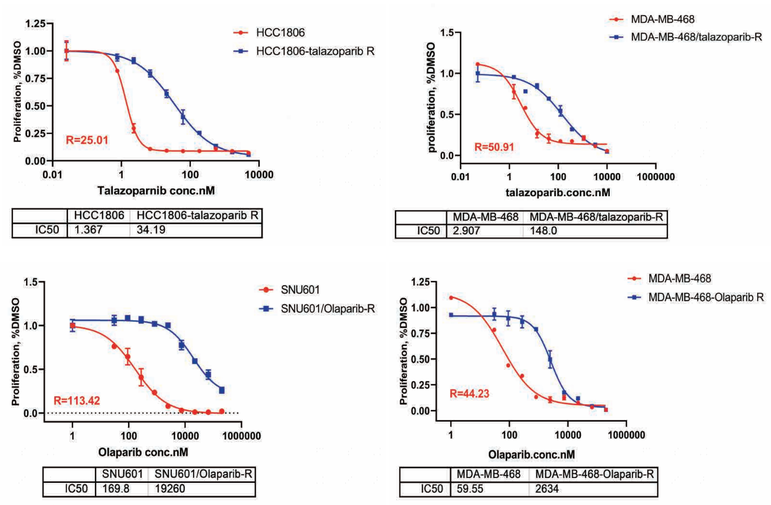
Cell Line	Double Time
MDA-MB-468 Talazoparib R	120h
MDA-MB-468 Olaparib R	76.8h
HCC1806-Talazoparnib R	21.9h
SNU-601 Olaparib R	55.0h

Figure 1: Microscopic morphology and doubling time of cells

During the process of in vitro cell culture, the growth and survival status of cells are determined by morphological changes under the microscope and changes in the passage cycle, providing accurate and objective statistical basis for "cell quality

Figure 2: Drug resistant index verification control".

3. Drug resistant index verification



	HCC1806	HCC1806-talazoparib R
IC50	1.367	34.19

	MDA-MB-468	MDA-MB-468/talazoparib-R
IC50	2.907	148.0

	SNU601	SNU601/Olaparib-R
IC50	169.8	19260

	MDA-MB-468	MDA-MB-468-Olaparib-R
IC50	59.55	2634

Figure 2: Drug resistance index was determined using IC_{50}

Drug resistance index was determined by comparison the IC50 between parental and resistant cell lines, the drug resistance index of HCC1806-Talazoparib R, SNU-601 Olaparib R, MDA-MB-468 Talazoparib R and MDA-MB-468 Olaparib R is 25.01, 113.42, 50.91 and 44.23, respectively.

4. Transcriptome sequencing analysis of drug-resistant strains

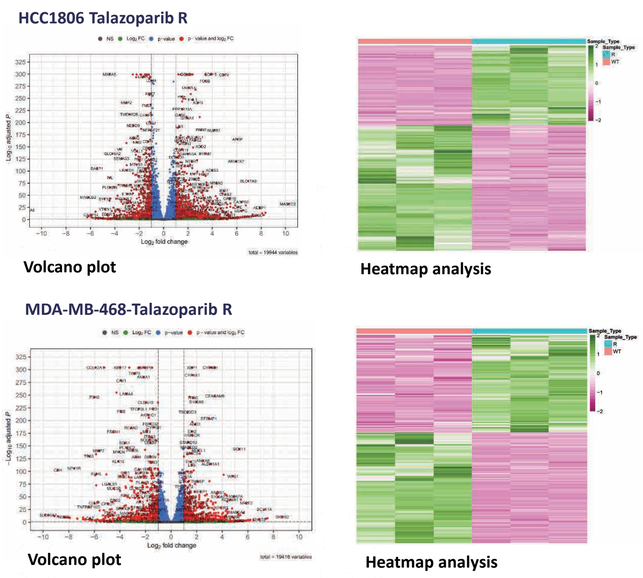


Figure 3: Transcriptome analysis of drug resistant cell lines with parental cell line.

Transcriptome analysis of drug-resistant cells indicates thousands of genes were influenced under drug resistant challenge. The differential genes expression profile may light a new hope for the anti-drug resistant cancer therapies.

5. Efficacy evaluation of DDR drug resistance CDX models

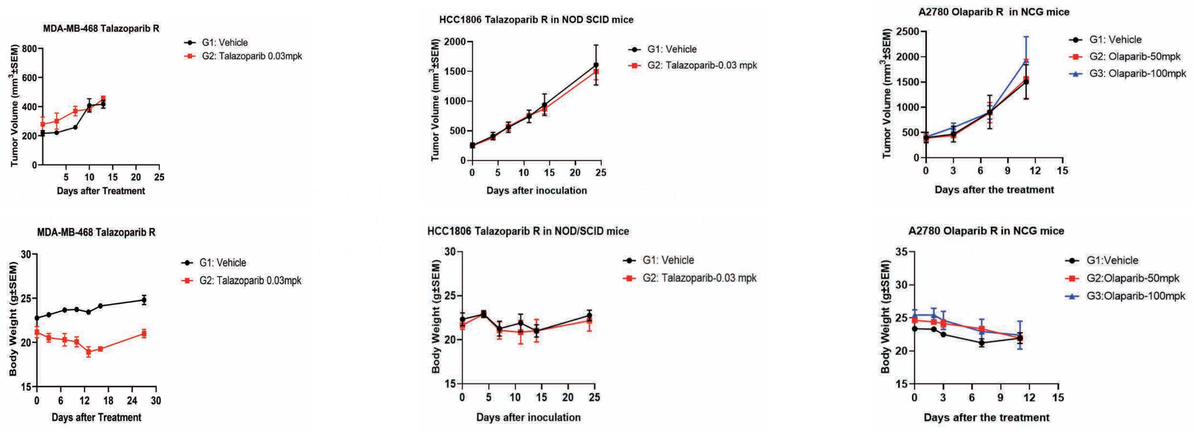


Figure 4: Efficacy of Talazoparib and Olaparib on specific drug resistant CDX models

The drug resistance of Talazoparib and Olaparib R CDX models were shown and indicated that each cell lines performed significant drug resistance to Talazoparib and/or Olaparib compared to that in parental cell line.

Summary

Our study underscores the significance of developing drug-resistant cell lines and CDX models in enhancing our understanding of cancer resistance mechanisms and facilitating the development of effective anticancer therapies. We induced resistance in ovarian and breast cancer cells by escalating drug concentrations in the culture medium, simulating clinical drug resistance. In vitro and in vivo assays were conducted to assess the impact of resistance on cell proliferation and drug efficacy. Transcriptome analysis identified differential gene expression between parental and resistant cell lines, offering insights into the molecular basis of resistance. These findings are instrumental for the future development of PARPi-resistant anticancer drugs, providing a Haiting Dai, Dan Zhou, Lan Xu,Ziwei Li, Jiali Liu, Huayi Qu, Wei Liu, Tiejun Bing, Wen Jen Yu In Vivo Pharmacology Center,ICE Bioscience Inc., Beijing, China foundation for designing novel therapeutics that can overcome or target resistant cancers.

References

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