192. Inhibitor for Treatment of Ovarian Cancer
(Yale University)

Asset Overview

Product Type	small molecule
Disease Area	Oncology
Indication	Ovarian cancer
Current Stage	Lead Optimization
Target	PARP inhibitor resistance
MoA	HR repair and sensitized HR repair proficient EOC to PARP inhibitors
Brief Description	• Poly ADP-ribose polymerase (PARP) inhibitors are promising targeted therapy for epithelial ovarian cancer (EOC) with BRCA mutations or defective homologous recombination (HR) repair. However, reversion of BRCA mutation and restoration of HR repair in EOC lead to PARP inhibitor resistance and reduced clinical efficacy of PARP inhibitors. • Triapine, a small molecule inhibitor of ribonucleotide reductase (RNR), impaired HR repair and sensitized HR repair proficient EOC to PARP inhibitors. • The discovery of a putative small molecule inhibitor of RNR and HR repair for combination with PARP inhibitors to treat PARP inhibitor-resistant and HR repair-proficient EOC.
Intellectual Property	WO2022221181A1
Publication	In silico screening identifies a novel small molecule inhibitor that counteracts PARP inhibitor resistance in ovarian cancer, Sci Rep. (2021)
Inventors	Z Ping LIN, Elena Ratner, Yong-lian ZHU

Highlights

- PARP inhibitors (PARPi) are FDA-approved targeted drugs for ovarian and breast cancers with BRCA mutations or homologous recombination (HR) repair deficiency.
- However, at least 50% of ovarian cancer has no HR deficiency and is resistant to PARPitherapy. Furthermore, PARPi-sensitive cancers can potentially restore HR repair and develop resistance to PARPi in patients.
- Dr. Elena Ratner's lab at Yale performed in silico screening and discovered a novel small molecule inhibitor DB4 that blocks HR repair and renders PARPi-resistant cancer cells hypersensitive to PARPi, such as olaparib and niraparib.
- Combination of DB4 and olaparib efficaciously suppresses the progression of PARPi-resistant ovarian cancer xenografts and significantly prolongs the survival time of mice.

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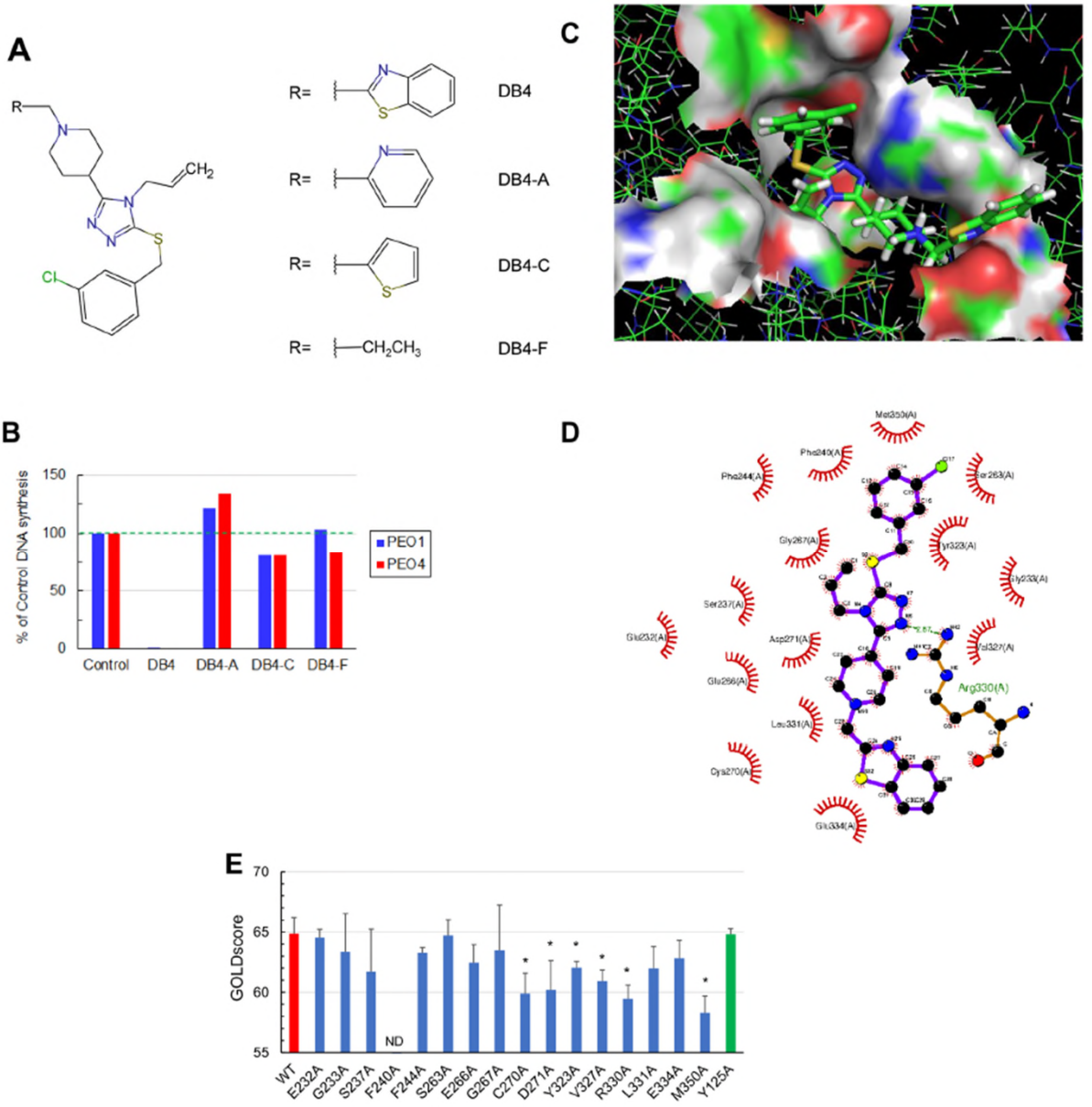
Key Data

SAR of DB4 analogs and molecular modeling of DB4 bound to the R2 subunit of RNR



(**A**) Structures of DB4 and its analogs, DB4-A, DB4-C, and DB4-F. (**B**) Effects of DB4 analogs on DNA synthesis. PEO1 and PEO4 cells were treated with 50 μM DB4 or analogs and assayed for DNA synthesis inhibition as described in Fig. 2B. The bivariate plots of Alexa Fluor 488 (EdU-positive) and PE-Cy5 (7-AAD-positive) are shown in Fig S1. The percentage of S phase cells treated with DB4 or DB4 analogs relative to the DMSO-treated control is calculated and shown. (**C**) Surface rendering of the triapine-binding pocket and a putative docking pose of DB4. Only residues putatively interacting with DB4 are displayed in surface rendering. (**D**) The schematic diagram of molecular interactions between DB4 and the triapine-binding pocket. The docking pose of DB4 shown in C was run by the LigPlot+ program to generate the 2-D representation of 1 hydrogen bond and 15 hydrophobic interactions with the binding pocket. (**E**) Effects of in silico mutagenesis of the triapine-binding pocket on the docking scores of DB4. Sixteen key amino acid residues were mutated to alanine using the PyMOL program. DB4 was re-docked into each of mutated triapine-binding pockets using the GOLD program. The GOLDScores of top-ranking docking poses similar to the wild-type (WT) control were averaged. Data are means ± SD (N = 3). *p < 0.05 compared with the WT control. *ND* no similar docking poses detected.

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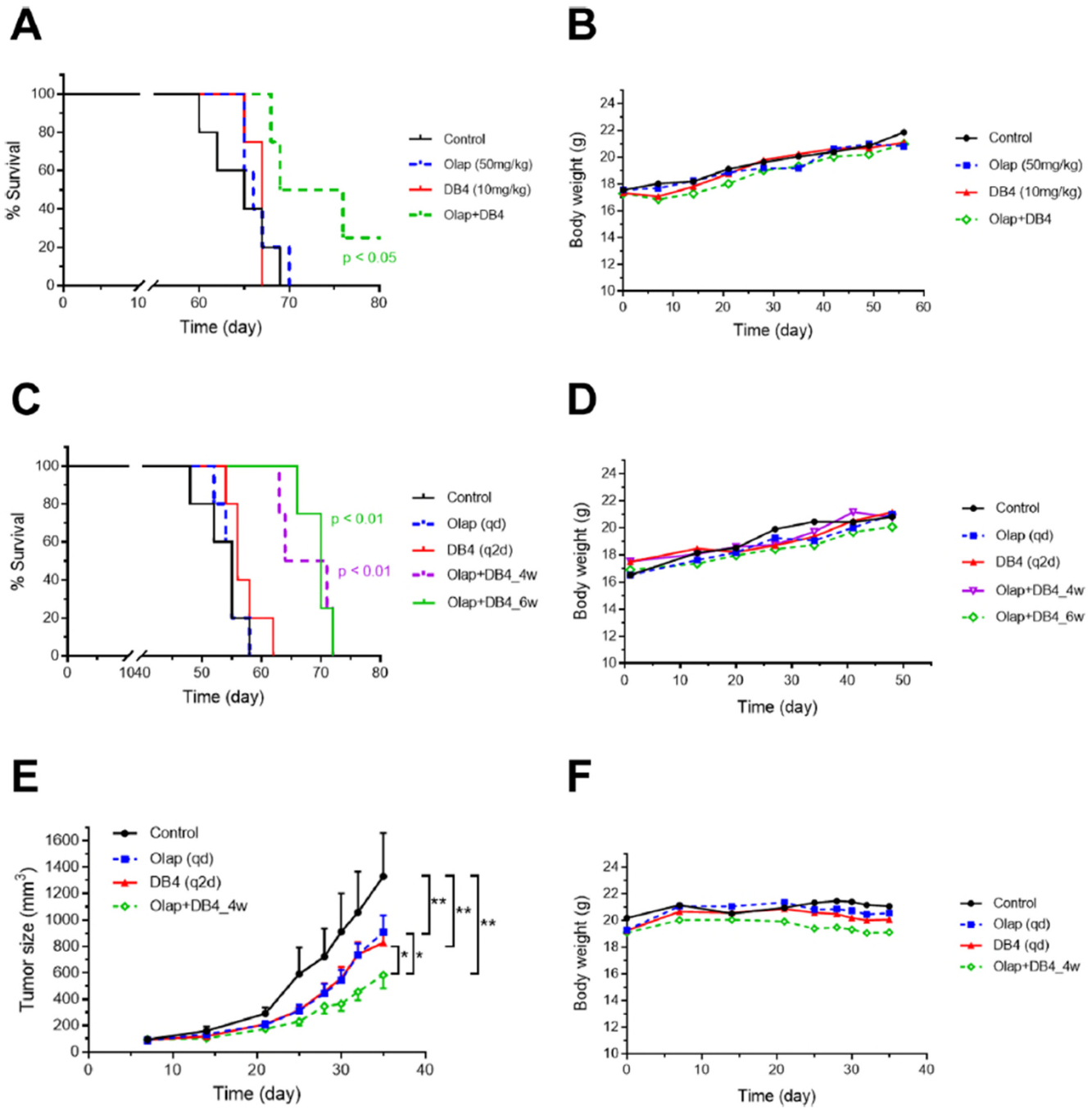
The combination of DB4 and olaparib suppresses the growth of BRCA-wild type EOC xenografs in mice.



(A) The DB4-olaparib combination causes significant prolongation of the survival time of SCID-beige mice bearing with PEO4ip xenografts. (B) The DB4-olaparib combination used in (A) exhibited no obvert toxicity to SCID-beige mice as determined by the body weight. (C) The modified DB4-olaparib combination furthers significant prolongation of the survival time of SCID-beige mice bearing with PEO4ip xenografts. (D) The DB4-olaparib combination used in (C) exhibited no obvert toxicity to SCID-beige mice as determined by the body weight. (E) The DB4-olaparib combination concertedly suppresses the sc growth of SKOV3 xenografts in mice. (F) The DB4-olaparib combination used in (E) exhibited no obvert toxicity to NCG mice as determined by the body weight.