

Technology Opportunity, Ref. No. UZ-22/762

TRIP12 and/or UBE2L3 inhibitor to increase responsiveness to PARP inhibitor

The invention relates to a method for determining the responsiveness to cancer treatment by administration of a PARP inhibitor and to a combination product including a PARP inhibitor and agent capable of decreasing or inhibiting or blocking TRIP12 and/or UBE2L3 activity for use in treatment of a tumour disease.

Keywords PARP inhibitors (Olaparib, Veliparib, Rucaparib, Niraparib, Talazoparib), Breast Cancer, Ovarian Cancer

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Reference [Gatti M, Imhof R, Huang Q, Baudis M, Altmeyer M. The Ubiquitin Ligase TRIP12 Limits PARP1 Trapping and Constrains PARP Inhibitor Efficiency. Cell Rep. 2020 Aug 4;32\(5\)](#) and [WO 2021/094426 A1](#) (Data and Patent on UBE2L3 not yet published)

Summary PARP inhibitors (PARPi) trap inactivated PARP1 on DNA, which is detrimental for cancer cell survival, in particular for cancers that are defective in DNA repair by homologous recombination (HR). Cellular regulators of PARP1 abundance and/or PARP trapping may thus determine the efficiency of PARPi. Degradation of target proteins by the ubiquitin pathway involves three kinds of enzymes: a general ubiquitin-activating enzyme (E1), which binds to the lysine residues of ubiquitin; a ubiquitin conjugating enzyme (E2), for example UBE2L3, which transfers ubiquitin onto target proteins; a ubiquitin ligase (E3), for example TRIP12, which interacts with target proteins such as PARP1 and confers the target specificity. The inventors found that UBE2L3 and TRIP12, via their ubiquitin transfer activities, regulate PARP1 levels and impact PARPi efficiency in cancer cells. Investigating the clinical relevance and the potential diagnostic and therapeutic value of UBE2L3/TRIP12-controlled PARPi efficiency may open new possibilities for cancer patients both with and without HR defects to potentially benefit from PARPi therapy.

Data Status: in vitro

Patent Status 2 EP Patent Applications pending

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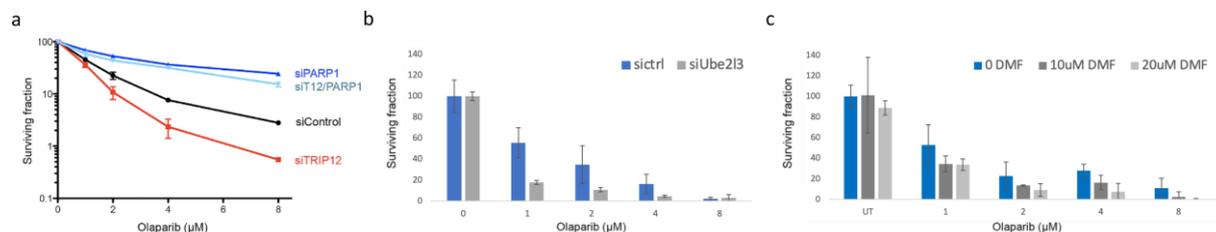


Figure 1: Sensitization of cancer cells to PARPi by blocking UBE2L3/TRIP12. (a) MCF-7 cancer cells are sensitized to PARPi Olaparib by downregulation of TRIP12. The effect is rescued by co-depletion of PARP1. (b) U2OS cancer cells are sensitized to PARPi Olaparib by downregulation of UBE2L3. (c) U2OS cancer cells are sensitized to PARPi Olaparib by the putative UBE2L3 inhibitor dimethyl fumarate (DMF).