134. Inhibitors of PARP1/2

(University of Colorado)

Asset Overview

Product Type	Small Molecule
Disease Area	Oncology
Indication	Cancer
Current Stage	Lead Optimization
Target	PARP, HPF1
MoA	Inhibit PARP activity, HPF1 activity, and the activity of the PARP-HPF1 complex
Brief Description	• The inventors developed a series of novel PARPi compounds which interact with PARP1/2 and HPF1 to form ternary PARP-HPF1 inhibitor complexes. • These novel PARPi compounds are configured to interact with HPF1 form more stable and effective inhibitors. • The novel PARPi can inhibit PARP activity, HPF1 activity, and the activity of the PARP-HPF1 complex. The novel PARPi can be therapeutically administered to treat cancers deficient in homologous dependent DNA double strand break repair pathways, vascular disease, as well as cerebral and cardiovascular neurotoxicity.
Intellectual Property	-
Publication	Inhibitors of PARP: Number crunching and structure gazing, PNAS (2022)
Inventors	Johannes Rudolph, Karen Jung, Karolin Luger

Highlights

- The combined data for inhibition of PARP2 by PARPi yield values for olaparib and rucaparib (median = 0.2 to 0.3 nM) that are noticeably more potent than those for PARP1. In contrast to PARP1, talazoparib is not significantly more potent than olaparib toward PARP2 (median = 0.2 nM). As for PARP1, niraparib and veliparib (median = 2 to 4 nM) are less potent than the other three PARPi. We discuss these differences in apparent affinities of the different PARPi for PARP1.
- Most breast cancers are not BRCA1/2 and thus do not show any special sensitivity to PARPi. In fact, many of these cell lines are defective in TP53BP1, which can promote partial restoration of HR and resistance to PARPi.
- Leukemias as a whole, and most especially B cell leukemias, are more sensitive to PARPi compared to most other cell lines and further investigation of this lead in preclinical and clinical studies seems warranted.
- Therapy for cancers deficient in homologous dependent DNA double strand break repair pathways
- Treatment for neurodegenerative and vascular diseases

134. Inhibitors of PARP1/2: A Treatment Approach for BRCA

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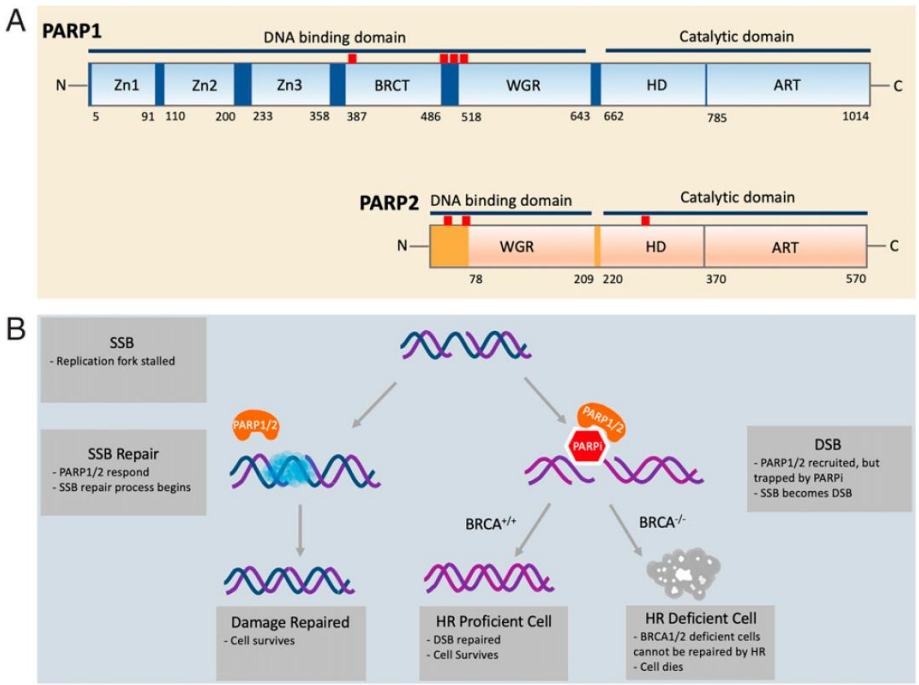
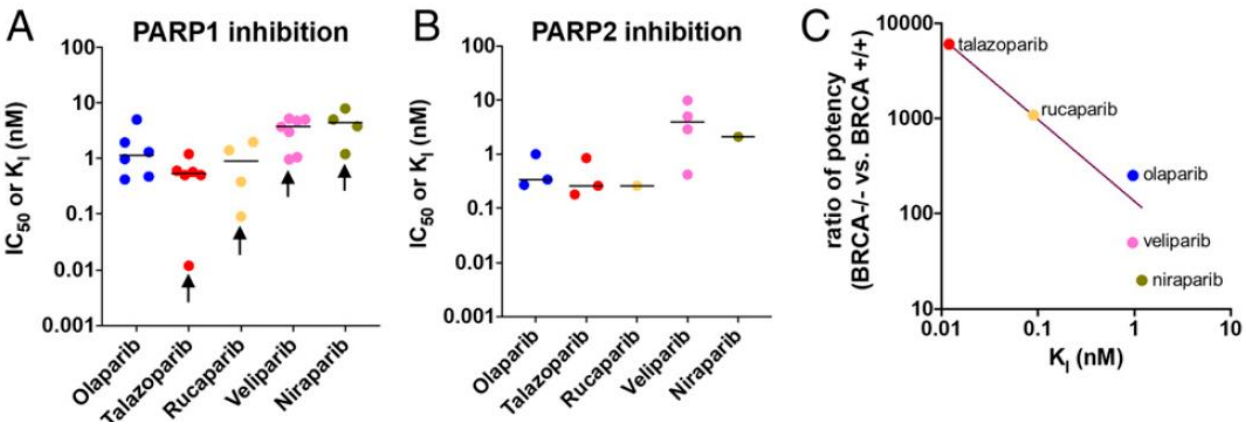
Key Data

Domain structure of PARP1 and PARP2, The mechanism of synthetic BRCA1/2 deficiency and PARPi



Inhibition measurements for PARPi with PARP2



(A) For PARP1, each reported IC50 and KI value is shown as a point and the line indicates the median value. Our reported measurements for all these inhibitors using a method that avoids the tight binding limit problem are indicated by black arrows. (B) For PARP2, each reported IC50 and KI value is shown as a point and the line indicates the median value. (C) The ratio of the median IC50 value for BRCT+/+ vs. matched BRCT/ cells is plotted against the KI as determined in ref. 65, since these values were determined with proper consideration of the tight-binding limit.