

Introducing More Potent PARP Inhibitors

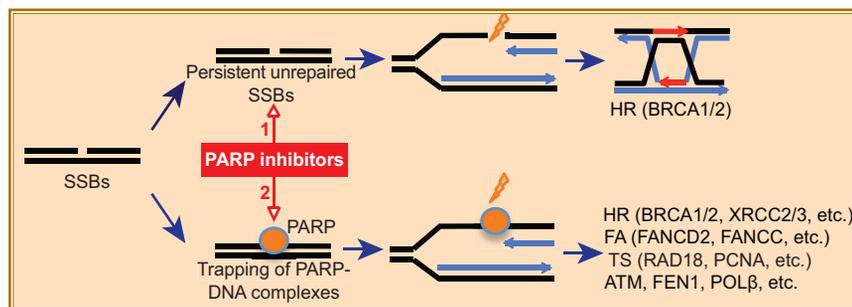
Scientists from CCR have made a discovery about how small molecules that target poly (ADP-ribose) polymerase—called PARP inhibitors—can stop cancerous growth. The findings, reported in *Cancer Research*, may allow clinicians to add more potent PARP inhibitors during treatment, according to the study's lead author, Yves Pommier, M.D., Ph.D., Chief of CCR's Laboratory of Molecular Pharmacology.

When a normal cell's DNA is damaged or mutated, several mechanisms and pathways can come into play to detect and repair the alterations. If the DNA is successfully repaired, the cell survives. If the DNA cannot be repaired, the cell undergoes a form of cellular suicide called apoptosis.

A protein that repairs damaged DNA is poly (ADP-ribose) polymerase, or PARP. When a strand of DNA is broken, or nicked, PARP moves to the damaged site and becomes activated.

Until the current study, PARP inhibitors were assumed to kill cancer cells by a process known as catalytic inhibition. These small molecule inhibitors prevent PARP from building its PAR polymer, a large, branched molecular bandage that wraps around damaged DNA and coordinates with nearby repair enzymes. PARP makes the polymer out of nicotinamide adenine dinucleotide (NAD⁺) building blocks, which bind to its catalytic site. Because PARP inhibitors also bind to that site, they block NAD⁺'s access. So the PAR polymer does not assemble, and DNA damage is not removed.

Preclinical studies of PARP inhibitors drew considerable interest because they induced apoptosis in



Dual cytotoxic mechanisms of PARP inhibitors. 1: Catalytic inhibition (upper pathway) interferes with the repair of DNA single-strand breaks (SSBs), leading to replication fork damage that requires homologous recombination (HR) repair. 2: Trapping of PARP-DNA complexes also leads to replication fork damage but utilizes additional repair pathways including Fanconi pathway (FA), template switching (TS), ATM, FEN1 (replicative flap endonuclease) and polymerase β .

BRCA-mutated breast tumor cells. These cells already have defective DNA repair, so it seemed that PARP inhibitors blocked an alternative repair pathway that *BRCA*-mutated cancer cells use to fix damaged DNA. Unable to harness that pathway, which is known as base excision repair (BER), breast cancer cells accumulated DNA damage and died. Consequently, PARP inhibitors moved on to clinical trials.

Catalytic inhibition is not the only way that PARP inhibitors slow cancerous growth, however. Pommier and his colleagues have now demonstrated that some PARP inhibitors also trap PARP on DNA by way of a poisonous "allosteric" effect.

"Our data show that when some PARP inhibitors bind to the NAD⁺ pocket, they tighten PARP binding to DNA," Pommier explains, "so their toxicity may be due to the poisonous complex that forms and prevents replication and transcription." He adds, "The PARP-DNA complex may also have more anticancer activity than catalytic inhibition."

Not all PARP inhibitors have this trapping ability. In fact, PARP-DNA complex formation depends heavily on the chemical structure of the

PARP inhibitor. Of the three drugs tested by the CCR research team, in collaboration with James Doroshow, M.D., Deputy Director for Clinical and Translational Research at NCI, only olaparib and niraparib were capable of both catalytic inhibition and PARP poisoning. Another drug, velaparib, was primarily a catalytic inhibitor.

According to Pommier, this helps to explain why velaparib is less cytotoxic to cancer cells than the other two drugs, despite having a similar ability to inhibit PARP's catalytic activity. It suggests that while olaparib and niraparib may be powerful enough for use as single-agent monotherapy, velaparib may be better suited to combination treatments.

Pommier emphasizes that while PARP inhibitors have been developed primarily for *BRCA1*- and *BRCA2*-mutant cancers, they may also be clinically useful in cancers associated with other types of DNA repair deficiency.

To learn more about Dr. Pommier's research, please visit his CCR Web site at <http://ccr.cancer.gov/staff/staff.asp?name=pommier>.

(Image: Y. Pommier, CCR)