Combination Cancer Therapy Involving the Chronic Use of Low Doses of ATR Signaling Inhibitors

Published date: Oct. 5, 2018

Technology description

This invention describes combination cancer therapy involving the chronic use of low doses of ATR signaling inhibitors, in combination with PARP inhibitors (or other genotoxic drugs) for increased efficacy, including against cancers unresponsive to PARP inhibitors alone.

ATR kinase is known to be critical for genome maintenance. It is also well known in cancer cells, to enable them to withstand increased replication stress caused by oncogenes. In fact, many ATR-specific inhibitors are currently in clinical trials for cancer treatment.

While previously known that ATR signaling enhances a cell’ s ability to use homologous recombination (HR)-mediated repair of DNA, short-term treatment with ATR inhibitors on HR were found to be modest. In the current invention, the Smolka lab has established that

(i) cancer cells exhibit a strong dependency on ATR signaling for maintaining the abundance of key HR factors and

(ii) chronic low doses of ATR signaling inhibitors depletes key HR factors, converting such treated cancer cells to mimic “BRCAness” (ie. dysfunctional BRCA1 or BRCA2)

These findings lead to the strategy of combining chronic, low dose inhibition of ATR signaling in cancer cells with PARP inhibitors, which are known to be effective against “BRCAness” cells. The figure on the next page shows the efficacy of employing this strategy against multiple cancer cell lines, including against cancer cells unresponsive to PARP inhibition alone (panel B).

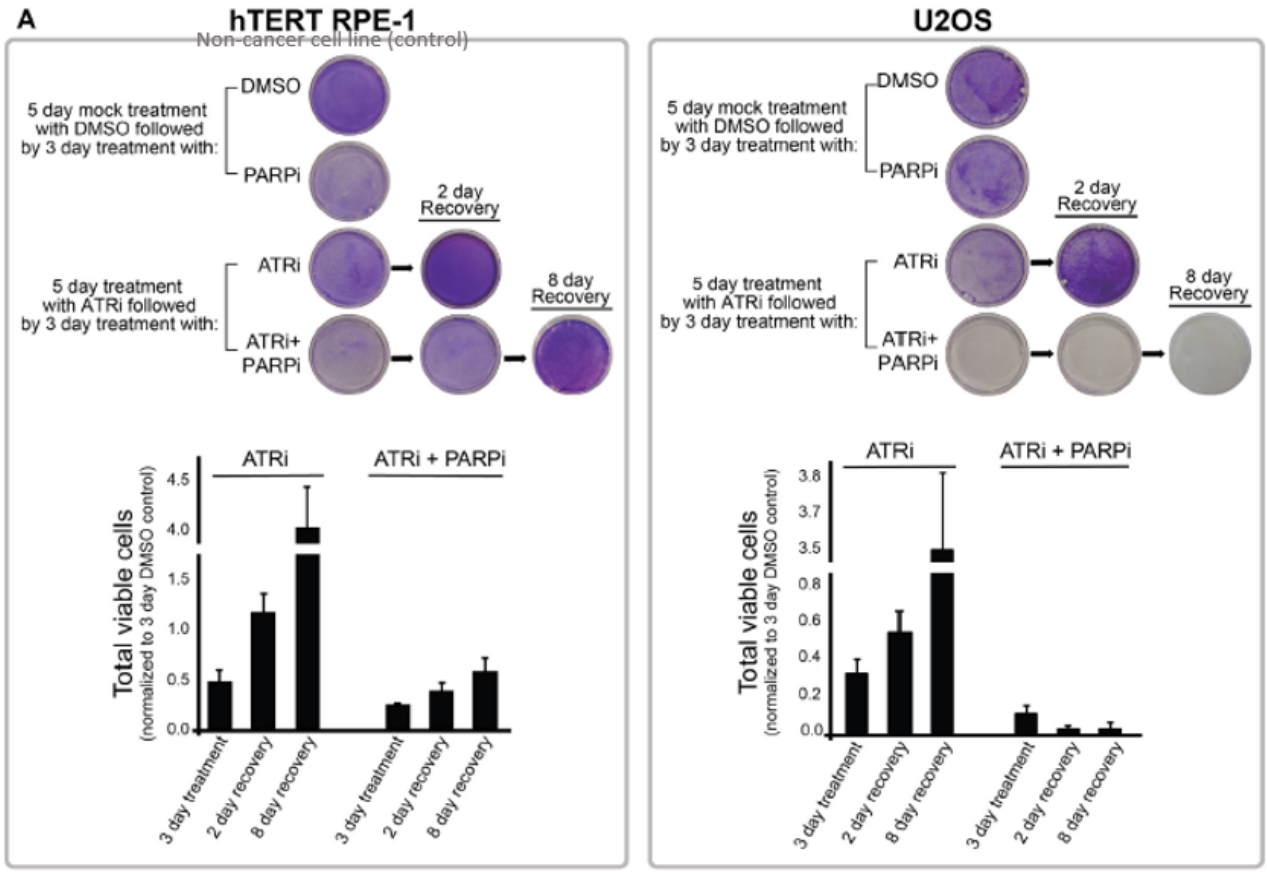


Figure A shows the efficacy of the chronic use of ATR signaling inhibitors in combination with PARP inhibitors.

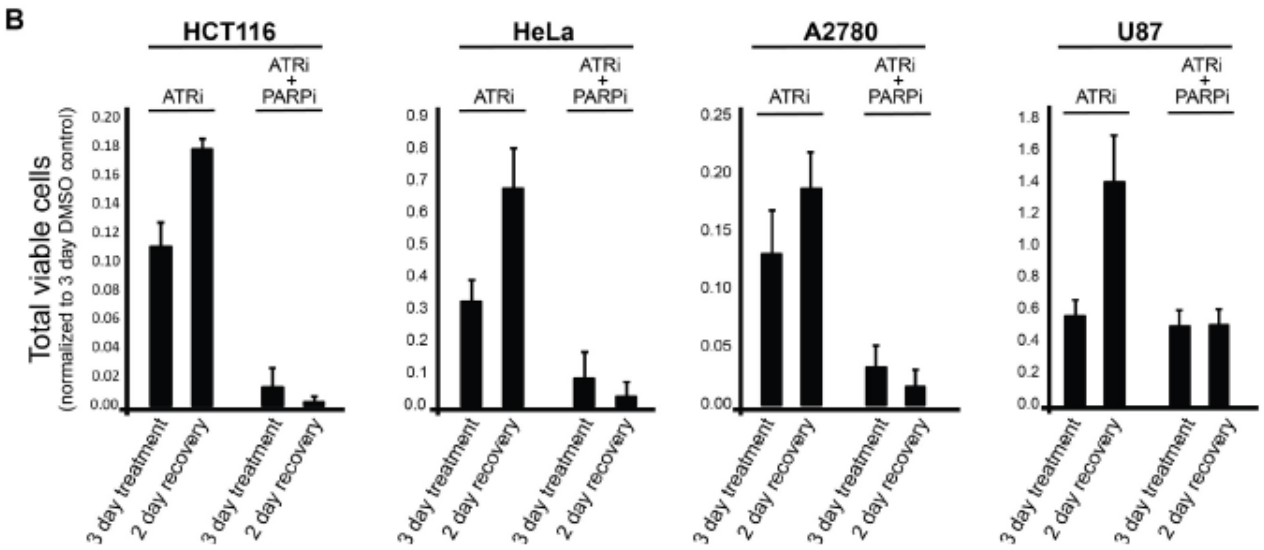
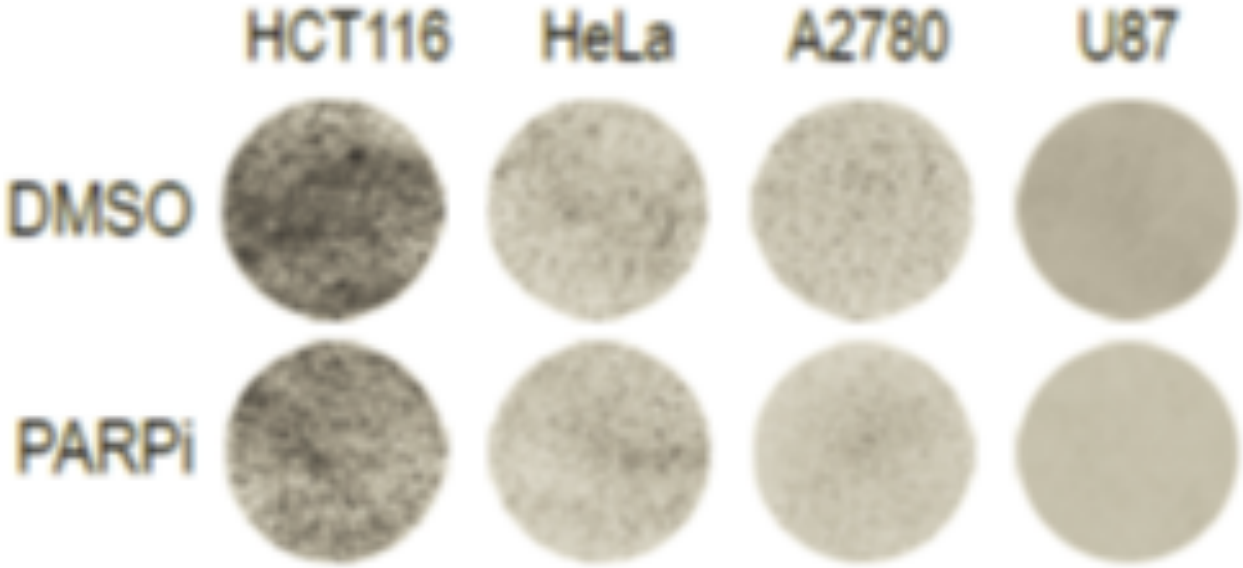


Figure B shows the efficacy of the chronic use of ATR signaling inhibitors in combination with PARP

inhibitors against cells unresponsive to PARP inhibitors alone as shown in the panel below.



Publications

US Provisional Patent Application

Kim D, & al. (2018). ATR-mediated proteome remodeling is a major determinant of homologous recombination capacity in cancer cells. **Nucleic Acids Res.** Online **.**

" Study reveals how promising cancer drug works for best use " Cornell Chronicle, July 23, 2018.

Application area

Novel combination cancer therapies involving ATR signaling inhibitors.

Advantages

Increased efficacy, including against more cancer types

Increased selectivity for cancer cells (higher efficiency for killing cancer cells with minimal or no impact on normal cells);

Lower doses of ATR signaling inhibitors needed, decreasing potential side effects.

Institution

Cornell University

Inventors

Marcus Smolka

Dongsung Kim

联系我们

叶先生

电 话：021-65679356

手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com