Weill Cornell Medicine

Improving the Efficacy of PARP1 Inhibitors by Targeting the Tumor Stroma

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Background & Unmet Need

- Poly (ADP-ribose) polymerase (PARP) inhibitors are a class of cancer drugs which are commonly used to treat BRCA1/2 mutant ovarian and breast cancers
- However, resistance to PARP1 inhibitors is common, with more than 40% of BRCA1/2 mutant patients not responding to therapy[1]
- The tumor microenvironment is implicated to be a driving factor of tumor progression and treatment resistance, and activation of cancer-associated fibroblasts (CAFs) can affect treatment outcomes
- P62 is a master regulator of CAF activation, and downregulation of p62 has been shown to promote CAF phenotype in tumor stroma
- However, the mechanism by which p62 is downregulated in tumors remains unclear
- **Unmet Need:** Methods of inhibiting the activation of the tumor microenvironment, especially CAFs, for improved therapeutic effect and duration

Technology Overview

- **The Technology:** Combination therapies to increase the effectiveness of PARP1 inhibitors by inhibiting activation of tumor stroma and CAFs
- **The Discovery:** PARP1 inhibitors generate a feedback loop that activates CAFs by downregulating master regulator p62
- Therefore, combination treatment with a PARP1 inhibitor and an inhibitor of stromal activation may revert stroma activation and enhance anti-tumor activity
- **PoC Data:** Treatment with a stroma-targeted hyaluronidase significantly enhanced olaparib antitumor activity both *in vitro* and *in vivo* models of prostate cancer
- This co-targeting mechanism is applicable in additional cancers such as lung, breast, and endometrium and for combinations of PARP1 and other stromal inhibitors, such as anti-TNFa, IL-6, and JAK molecules

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Patents:
PCT Application Filed

Publications:
Linares et al. *Cell Rep*. 2022.

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[1]Li et al. *Mol Cancer*. 2020.

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Technology Applications

- Combination therapy of PARP1 inhibitor with drugs targeting TNFalpha, IL-6, or Janus kinase (JAK)
- Combination therapy of PARP1 inhibitors with other drugs that target the stroma, such as hyaluronan (HA) synthase inhibitors, fibroblast activation protein alpha (FAPα) inhibitors, SMO-inhibitors, CXCL12 antagonists, or DDR2 inhibitors

Technology Advantages

- Combination therapy improves efficacy of PARP1 inhibitor therapy
- May reduce refractory rates of treatment with PARP1 inhibitors

Supporting Data / Figures

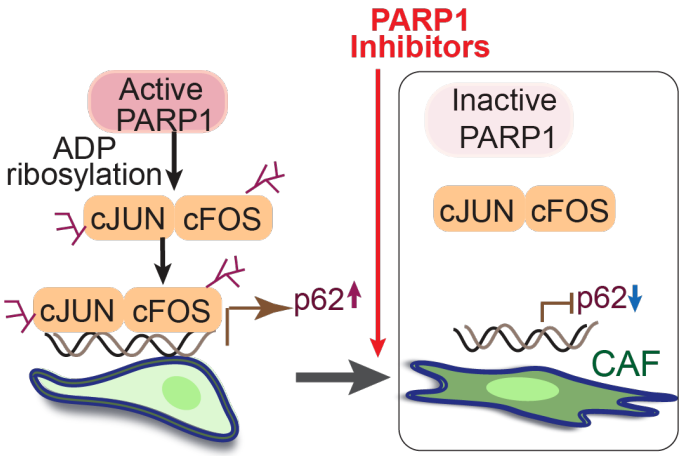

Figure 1: Schematic depicting how PARP inhibitors activate CAFs.

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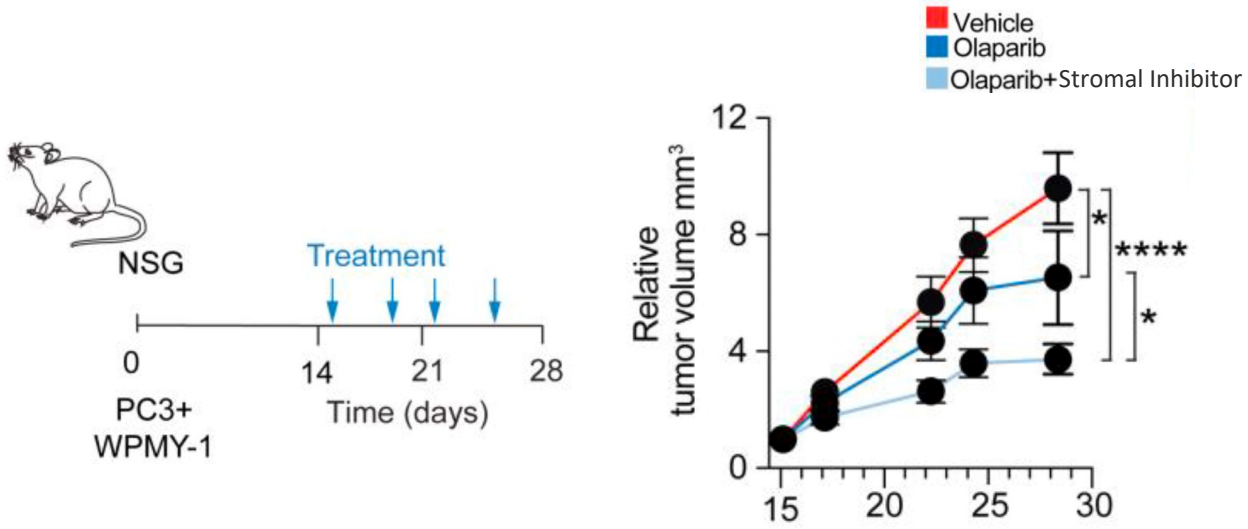

Figure 2: Left: Subcutaneous xenograft co-implantation in NSG mice of PC3 PCa cells with WPMY-1 cells. Mouse were treated twice a week with Olaparib 40 mg/Kg or Olaparib + Stromal Inhibitor for 2 weeks. **Right:** Stromal activation blockade reduces the tumor supporting effects of Olaparib.

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