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-TNFα, IL-6, and JAK molecules.

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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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**Patents:**
- PCT Application Filed

**Publications:**

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**Cornell Reference:**
- D-10168
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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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