Eliciting BRCA deficiency in Triple Negative Breast Cancer Cells for Enhanced Chemoradiation using Pluronic Nanoparticles

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**BACKGROUND**

- Triple Negative Breast Cancer (TNBC) cells are defined by their lack of 3 receptors: estrogen (ER), progesterone (PR), and human epidermal growth factor receptor (HER2).
- Treatment options include surgery, radiation, and chemotherapy not targeted therapies.

**OBSERVATION, HYPOTHESIS, & AIMS**

- When BRCA is mutated, cells rely on less efficient, secondary DNA repair proteins such as poly-ADP ribose polymerase (PARP).
- Administration of a phosphoinositide 3-kinase inhibitor (PI3K) has been shown to down regulate BRCA expression.

Hypothesis: Nanoparticle co-administration of a PARP and PI3K inhibitor will provide an alternate therapy for the 80% of TNBC patients who do not have a BRCA mutation and will reduce the toxic off-target effects often seen by chemotherapy.

**CELL LINES & INHIBITORS**

<table>
<thead>
<tr>
<th>Cell line</th>
<th>BRCA1</th>
<th>PI3K</th>
<th>Tatrazolamide (PARP)</th>
<th>Buparlisib (PI3K)</th>
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<tbody>
<tr>
<td>MBA MB 465</td>
<td>normal</td>
<td>mutation</td>
<td>1μM</td>
<td>1μM</td>
</tr>
<tr>
<td>BT549</td>
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<td>1μM</td>
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<tr>
<td>BT20</td>
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<td>mutation</td>
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<tr>
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<td>&gt;10μM</td>
<td>&gt;10μM</td>
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<td>normal</td>
<td>&gt;10μM</td>
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</tr>
</tbody>
</table>

**CONFIRMING INHIBITOR ACTIVITY & EFFICACY**

**A. BRCA1 Protein Expression**

**B. PADPR Protein Expression**

**C. High Density Survival Assay**

**CELL CYCLE ANALYSIS**

- MDA MB 465 cells treated with mocodazole (2μM phase inhibitor), PARP inhibitor (1 μM), or PI3K inhibitor (1 μM) were analyzed for DNA content and compared to an untreated control. Treatment with a PARP inhibitor increases the amount of cells in S phase and G2 indicating a G2/M arrest. PI3K treatment shows no difference from control.

**NANOPARTICLE FORMULATION & CHARACTERIZATION**

- A. Nanoparticle Formulation
- B. TEM
- C. DLS
- D. Drug Release

**CONCLUSIONS & FUTURE DIRECTIONS**

- PI3K inhibitor down regulates BRCA
- PARP inhibitor effectively inhibits PARP
- Microfluidic platform effectively forms and loads (~50%) Pluronic micelles
- Flow cytometry to determine treatment effect on cell cycle
- Analyze γH2AX formation in response to various treatment protocols
- Repeat High Density Survival Assay at lower drug concentration
- Investigate radio-responsive polymers and/or excipients for enhanced formulation

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**REFERENCES**