**Abstract # 3221**

**Kevetrin induces p53-dependent and independent cell cycle arrest and apoptosis in ovarian cancer cell lines representing heterogeneous histologies**

Ashok Kumar1, David P. Brennan1, Ramita Chitré Pechet2, Sylvia A. Holten3, Sya Ham3, Geoffrey I. Shapiro4, Krishna Menon5

1Cellectes Corporation, Beverly, MA, 2dana-Farber Cancer Institute, Boston, MA

**Introduction**

Ovarian cancer (OC) is a molecularly and histologically heterogeneous disease. However, standard treatment is the same for all subtypes. High systemic relapse rates, and sensitivity to genotoxic treatments, are major concerns. Current treatments are limited in their ability to improve patient outcomes and the cause of treatment failure is often attributed to chemotherapeutic resistance. Chemotherapeutic drug resistance in ovarian cancer is a complex process involving multiple signaling pathways. Apoptosis is a vital process involving the regulation of cell cycle checkpoints, cell death, and DNA repair. Understanding pathways involved in resistance to genotoxic drugs can provide novel targets for therapeutic intervention.

In this study, we evaluated the effects of Kevetrin, a small molecule inhibitor of Aurora A, on the p53 signaling pathway in ovarian cancer cell lines representing heterogeneous histologies. We aimed to elucidate the critical role(s) of Aurora A in the p53 signaling pathway and identify potential therapeutic targets.

**Methodology**

We treated and loaded samples from 3 cell lines (A2780-p53 wild type, OVCAR-3-p53 mutant, OVCAR-3-p53 partial deletion) representing heterogeneous histologies with Kevetrin or vehicle controls. The effects of Kevetrin treatment were evaluated using Fold change analysis in mRNAseq studies. Furthermore, using KEGG pathway analysis, we identified potential therapeutic targets for ovarian cancer.

**Key Findings**

**Table 1: Fold change of key genes**

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Gene name</th>
<th>Pathway</th>
<th>Pathway name</th>
<th>Fold change</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCNE2</td>
<td>cyclin E2</td>
<td>KEGG</td>
<td>p53 signaling pathway</td>
<td>0.26</td>
</tr>
<tr>
<td>MDM2</td>
<td>Mdm2, p53</td>
<td>KEGG</td>
<td>p53 signaling pathway</td>
<td>6.94</td>
</tr>
<tr>
<td>FAS</td>
<td>Fas (TNF receptor superfamily, member 6)</td>
<td>KEGG</td>
<td>p53 signaling pathway</td>
<td>4.59</td>
</tr>
</tbody>
</table>

**Results Summary**

- Kevetrin-induced apoptosis in wild type p53, mutant p53 and partially deleted p53 ovarian cancer cell lines as analyzed by Fold change of mRNA.
- Elevated wild type p53 and decreased p53 wild type gene expression after 48 hours in OVCAR-3 cell line.
- Kevetrin increased p53 wild type gene expression and decreased p53 mutantgene expression in A2780 cell line.
- Increased p53 wild type mRNA expression in OVCAR-3 cell line.
- Significant changes were observed in wild type p53 mRNA.
- In xenograft model, Kevetrin inhibited all tumor growth, and increased SKOV-3 bw tumor tumor.
- Transcriptional analysis demonstrated that Kevetrin modulates p53 signaling in ovarian cancer cell lines as well as xenograft tumor xenografts by RNAseq studies.

**Conclusions**

- Kevetrin modulates p53 signaling pathway in ovarian cancer cell lines as shown in the mRNAseq study.
- Further detailed mechanistic studies are ongoing.

**Further Information**

Cellectes Corporation
7142 Corporate Dr, Suite 151
Beverly, MA 01915