1. The majority of women diagnosed with advanced-stage epithelial ovarian cancer (OC) experience tumor recurrence associated with the development of chemoresistance, and platinum-resistant OC is uniformly fatal.

2. Decoycytosine methylation of CpG islands in promoter regions of tumor suppressor genes (TSGs) plays a prominent role in the development and progression of drug-resistant OC. Genes known to be silenced by methylation in OC include MLH1, RASSF1A, BRCA1, HOX genes, and others.

3. Based on preclinical studies generated by our group demonstrating that inhibition of DNA methylation reverses platinum resistance in EOC cells, we designed and recently completed a phase I/II trial using the DNA methylation inhibitor decitabine (5-aza-2'-deoxycytidine) in combination with carboplatin in patients with recurrent, platinum-resistant OC (Fang et al., Cancer, 2010; Matei, et al., Cancer Research, in press).

4. This trial demonstrated that repetitive low-dose decitabine is well tolerated when combined with carboplatin (Fang et al., Cancer, 2010) and has biological (i.e., DNA-hypomethylating) as well as clinical activity (Matei, et al., Cancer Research, in press). These results support the concept that therapies targeting epigenetic changes can be employed for clinical benefit in EOC.

5. SGI-110 (Astex Pharmaceuticals, Inc.) is a DNA hypomethylating agent with demonstrated activity in restoring silenced TSG expression in cancer cells by reversal of DNA methylation.

6. As a decitabine-deoxycytosine dinucleotide, SGI-110 has been shown to be less prone to deaminase and could have advantages over decitabine, such as better stability, less toxicity and a more convenient and less frequent SQ administration.

**HYPOTHESIS AND OBJECTIVES**

- Our group’s long-term goal is to establish interventions targeting the epigenome as a new therapeutic strategy for ovarian cancer.
- We hypothesize that epigenetic modulators in combination with platinum will exert potent antitumor activity in preclinical models of treatment naïve and resistant, recurrent OC.
- We examined the ability of SGI-110 to resensitize cisplatin-resistant ovarian cancer cells by demethylating and derepressing of drug-response genes and inhibit OC cell proliferation in vitro and in vivo.
- We conducted a ‘tolerability’ study to examine that SGI-110 is active in non-tumor bearing mice.
- We investigated the ability of SGI-110 to reverse aggressive ovarian cancer by targeting ovarian cancer stem cells and associated molecular pathways, including epithelial-mesenchymal transition (EMT) and transforming growth factor-beta (TGF-β).

**METHODS**

**RESULTS**

**CONCLUSIONS**

1. SGI-110 is tolerable in combination with cisplatin in mice.
2. LINE1 and gene specific (AXIN1, RASSF1A) demethylation is achieved in vivo in PBMCs and xenografts.
3. SGI-110 resensitizes ovarian cancer cells to platinum.
4. SGI-110 reduces the number of ALDH+ cells.
5. SGI-110 prevents TGF-β-induced EMT by effects on E-cadherin expression and indirectly by affecting expression of EMT regulators Zeb1/2 and miR-200.
6. SGI-110 combined with platinum warrants further study in clinical and preclinical models of ovarian cancer.