**A Novel Septin inhibitor for the Treatment of Endometrial Cancer**

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**Background:** Endometrial cancers are frequently associated with HER2 amplification or mutations on FGFR2, PI3K/AKT, KRAS/ERK and WNT/β-catenin signaling pathways. This allows for the survival and growth of endometrial cancer cells.

Septins are associated with cancer cell proliferation, epithelial-to-mesenchymal transition, cellular migration, cellular invasion and chemotherapy resistance. Tumors that have altered expression of septins are associated with decreased survival rates in cancer patients. FCF is the only septin inhibitor available, but it is highly toxic.

**Methods:** Septin paralogs were analyzed for their expression and correlation to mortality in endometrial cancer patients. Sulforhodamine B (SRB) cell proliferation assay was used to analyze the anti-proliferative effect of UR214-9 in ECC-1 and AN3CA endometrial cancer cell lines. Western blots were performed on KLE and AN3CA cell lines to determine if UR214-9 can alter oncogenic signaling pathways.

**Results:** Of all 13 septin paralogs (sept1-12 and sept 14) sept2, 6, 7, 8, 9, 10 and 11 were found to be upregulated in endometrial cancer. Among those septins, overexpression of sept2, 8, 10 and 11 correlated with increased patient mortality ($p < 0.05$) while expression of other septins (6, 7 or 9) was statistically insignificant ($p > 0.05$). Our laboratory developed novel small molecule septin inhibitor through structural modifications of FCF. Of the 9 FCF analogs developed, UR214-9 was found to be the most potent septin inhibitor. It was shown to decrease cell proliferation of endometrial cancer cell lines ECC-1 and AN3CA, downregulate expressions of HER2 and β-catenin and inhibit the activation of ERK (a downstream target of HER2, FGFR2 and/or KRAS) in KLE cells, and inhibit phosphorylation of FRS2α (a direct substrate of FGFR) in FGFR2 mutant AN3CA cells.

**Conclusion:**

Endometrial cancer is associated with septin overexpression and upregulation of key pathways in endometrial cancer. Our lab developed a drug (UR214-9) that decreased cell proliferation in ECC-1 and AN3CA cell lines, downregulated the expression of HER2, FGFR2, and KRAS in KLE cell lines, and inhibited FR2S α in AN3CA cell lines.