NIH Award from the Eunice Kennedy Shriver National Institute of Child Health and Human Development

Principal investigator: J. Julie Kim, obstetrics and gynecology, Feinberg School of Medicine

- **Project**: Mechanisms of Progesterone Receptor Action in Endometriosis
- **Start Date**: September 25, 2009
- **Total Award Amount**: $377,500

**How the results of this project will benefit society:**
Endometriosis affects more than 10 percent of women in the US and is often associated with persistent pelvic pain, and infertility. While progesterone antagonizes estrogen-mediated growth and promotes differentiation of the normal endometrium, ectopic endometriotic tissues respond inadequately to progesterone. We will investigate the role of progesterone in endometriotic cells and explore novel mechanisms of progesterone receptor action with the hopes of enhancing the responsiveness of the endometriotic cells to progesterone. Specifically, we will focus on the transcriptional role of the progesterone receptor with a member of the forkhead family of transcription factors, FOXO1. Since we have found that levels of FOXO1 are significantly diminished in endometriotic cells, we will investigate the effect of restoring levels of FOXO1 in these cells to determine whether this would increase the cells’ responsiveness to progesterone. These responses include enhanced differentiation and cell death. Understanding such molecular mechanisms that are associated with progesterone resistance in endometriosis will provide new opportunities for the development of alternate, innovative and desperately needed therapies.

**The problem the project is trying to solve:**
The long-term objective of this application is to better understand the phenomenon of progesterone resistance in endometriosis in order to develop alternate therapies for this disease. We have found that endometriotic cells not only inadequately respond to progesterone but that the AKT pathway is highly activated. In support of this, levels of FOXO1, a direct downstream target of AKT were significantly lower in endometriotic cells, presumably due to increased protein degradation. Since we have previously demonstrated that FOXO1 promotes cell cycle arrest and apoptosis in disease-free endometrial cells and that it synergizes with the progesterone receptor to promote differentiation, we hypothesized that decreased FOXO1 levels significantly contributes to the decreased responsiveness to progesterone and increased survival of endometriotic cells. In this study, we will investigate the effect of inhibiting the AKT pathway thereby increasing levels of FOXO1, on progesterone-mediated differentiation and cell death in endometriotic cells.

**How the project will work:**
This proposal consists of two aims. Specific aim 1 will explore the effect of restoring FOXO1 using overexpression vectors and chemical inhibitors to PI3K and AKT on progesterone-mediated differentiation and apoptosis in endometriotic cells. Specific aim 2 will focus on harboring human endometriotic tissues or cells under the kidney capsule of SCID mice in order to study the effects of an AKT inhibitor in the presence of progesterone on differentiation and apoptosis. These aims will increase the understanding of progesterone resistance in endometriosis as well as investigate the use of targeted biological agents for the development of new modalities of treatment for endometriosis.