ENDOMETRIOSIS: WHO IS THE CULPRIT, ESTROGEN OR PROGESTERONE?
Endometriosis affects 10% of reproductive aged females
- Difficult to treat
- Significant economic impact
- Chronic disease

Early stage disease is associated with peri-lesional scarring and advanced disease with prolific fibrosis
"There is little question that estrogen plays an important role in the pathogenesis of endometriosis" ~Sperroff Chapter 29

- Estrogen stimulates endometriosis
- Aromatase inhibitors cause its regression
- Estrogen production and metabolism are altered in endometriotic cells in ways that promote disease
  - Overproduction of estrogen in endometriotic stromal cells
“Whereas estrogen clearly aggravates endometriosis, the effects of progesterone are less clear”

- progestins can be effective for relieving pain, but SPRMs are also
- Endometriotic tissue produces a substantial amount of progesterone and has lower levels of PR
UTILIZING A GENETIC MODEL OF ENDOMETRIOSIS

- **KLF11**
  - Sp/KLF transcription factor
  - Associated with several endocrine and female reproductive tract diseases
    - DM
    - Fibroids
    - Endometriosis
    - Ovarian CA
  - Selectively diminished in human endometriosis lesions compared to eutopic uterine endometrium
  - KLF11-/- mice are associated with endometriosis disease progression and prolific fibrosis
A MURINE MODEL FOR ENDOMETRIOSIS

Endometrial implants

Parietal peritoneum

5 mm uterine segment
Endometriosis surgery was replaced by induction of sterile peritonitis.

This allowed us to study the fibrotic response in:
- males
- ovariectomized females (without subjecting them to multiple surgeries)
SEXUAL DIMORPHISM?

Sexual dimorphism is a phenotypic difference between males and females of the same species, such as differences in morphology, size, ornamentation and behavior.
SEXUAL DIMORPHISM

KLF11-/-

♀

KLF11-/-

♂

Intraperitoneal Chlorhexidine (IP CHX)

A

Average Fibrosis Score

*  

B

<table>
<thead>
<tr>
<th>Wild-type</th>
<th>Klf11-/-</th>
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E

Klf11-/- Female

F

Klf11-/- Male
WHAT CAUSED THIS DIMORPHISM?

- Y chromosome??
- Sex hormones??
KLF11-/- ♀ Intraperitoneal Chlorhexidine (IP CHX)

Ovariectomy

Sham Surgery

Intraperitoneal Chlorhexidine (IP CHX)
- Implicates sex hormones – estradiol and progesterone from the ovarian tissue

- But is one of these more important than the other?
KLF11-/- ♀

Ovariectomy

Estradiol injections

Intraperitoneal Chlorhexidine (IP CHX)

KLF11-/- ♀

Ovariectomy

Progesterone injections

Intraperitoneal Chlorhexidine (IP CHX)

KLF11-/- ♀

Ovariectomy

Testosterone injections

Intraperitoneal Chlorhexidine (IP CHX)
- Presence of progesterone (or estrogen+progesterone state) is important for the development of intraperitoneal fibrosis

- Is there any role for antiprogestosterone agents for preventing adhesion formation?
  - Mifepristone? Ulipristal?
KLF11-/− ♀ Intraperitoneal Chlorhexidine (IP CHX) Oil injections

KLF11-/− ♀ Mifepristone injections

KLF11-/− ♀ Ulipristal injections

Intraperitoneal Chlorhexidine (IP CHX)
What happens in males if you add in progesterone?
KLF11-/-
♂

Oil injections

Intraperitoneal Chlorhexidine (IP CHX)

Progesterone injections

Intraperitoneal Chlorhexidine (IP CHX)

Male Oil+CHX

Male Progesterone+CHX
Studies looking at mechanisms and fibrotic pathways on a in vitro level are underway utilizing gene expression through microarrays
Progesterone or Estrogen+progesterone environments can increase fibrotic progression when there is a stimulus for adhesion formation
- Endometriosis
- Post surgical adhesions
FEMALE PREDOMINANCE OF ADHESIVE DISEASE?

- Increased incidence of postoperative adhesion-induced intestinal obstruction

- Encapsulating peritoneal sclerosis more prevalent in premenopausal females
  - (Guest S 2009 Hypothesis: gender and encapsulating peritoneal sclerosis. Perit Dial Int 29:489-491)

- Pulmonary hypertension has also had a female predominance
Questions?