

# **Multi-organ, integrated female reproductive system for disease modeling and environmental exposure toxicity testing.**

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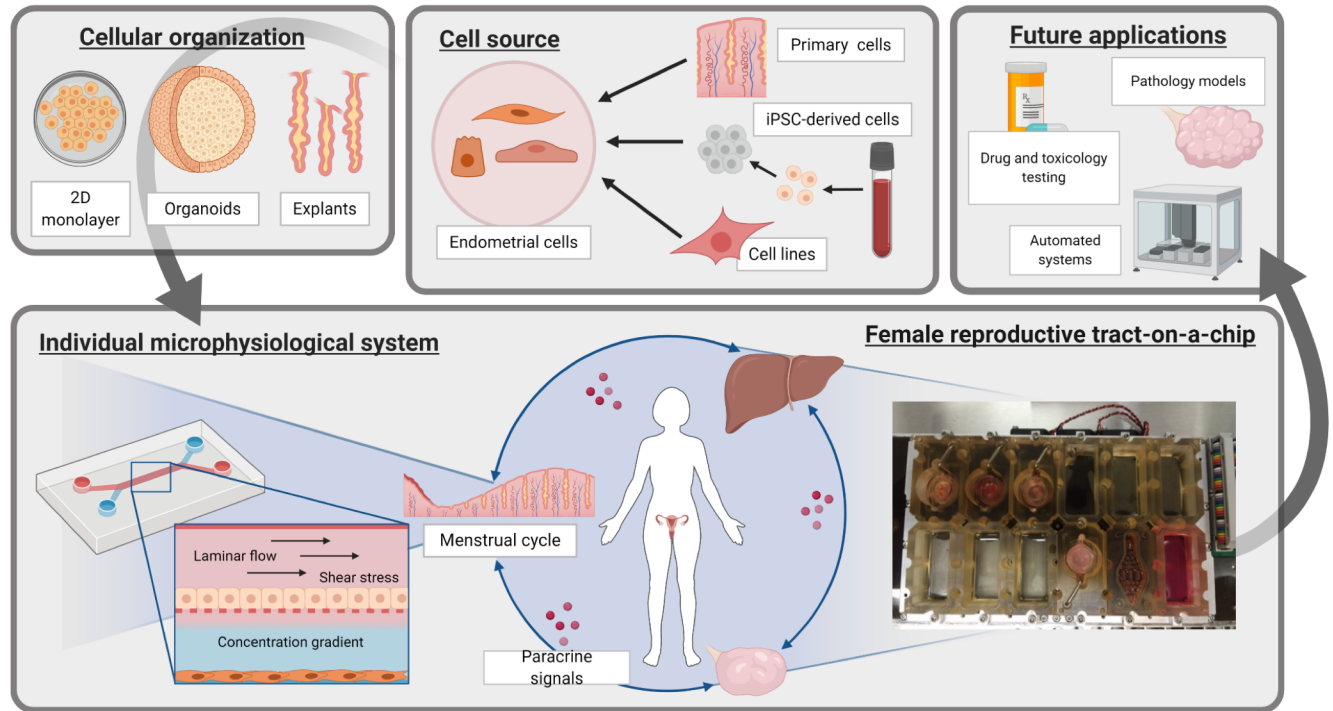
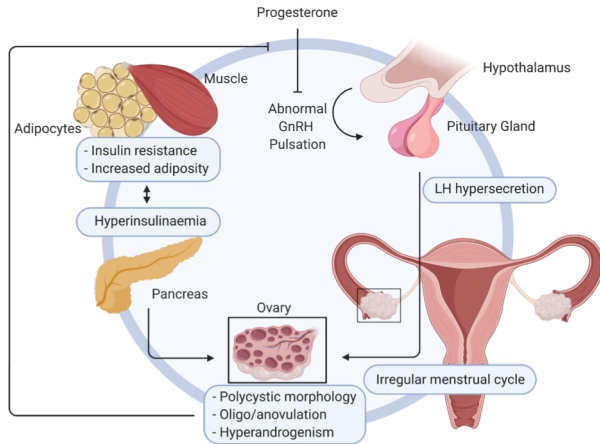
# Polycystic Ovarian Syndrome (PCOS)

- Most common endocrinopathy in reproductive age women (5-20%)
  - At least 5 million women (U.S.)
  - \$4.36 billion per year (U.S., 2005)

| NIH/NICHD                                                                                               | ESHRE/ASRM 2004 (Rotterdam criteria)                                                                          | Androgen Excess Society 2006                                                                            |
|---------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|
| Includes all of the following criteria:                                                                 | Includes two of the following criteria:                                                                       | Includes all of the following criteria:                                                                 |
| <ul style="list-style-type: none"><li>• Clinical and/or biochemical signs of hyperandrogenism</li></ul> | <ul style="list-style-type: none"><li>• Clinical and/or biochemical signs of hyperandrogenism</li></ul>       | <ul style="list-style-type: none"><li>• Clinical and/or biochemical signs of hyperandrogenism</li></ul> |
| <ul style="list-style-type: none"><li>• Menstrual dysfunction</li></ul>                                 | <ul style="list-style-type: none"><li>• Oligo-ovulation or anovulation</li><li>• Polycystic ovaries</li></ul> | <ul style="list-style-type: none"><li>• Ovarian dysfunction and/or polycystic ovaries</li></ul>         |



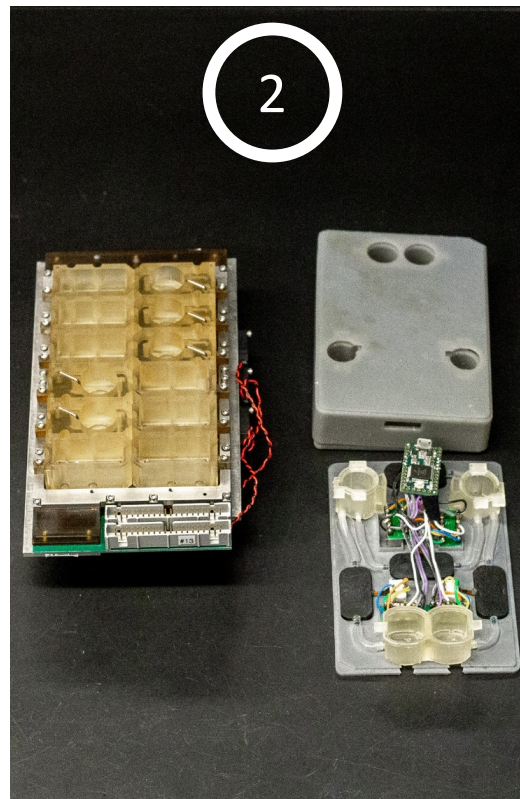
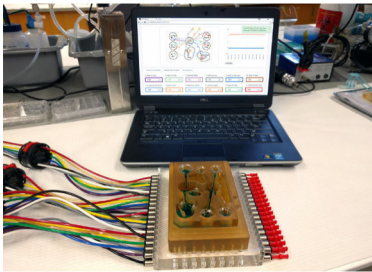
# PCOS impacts multiple organ systems



# Evolution of EVATAR to Blac Tie

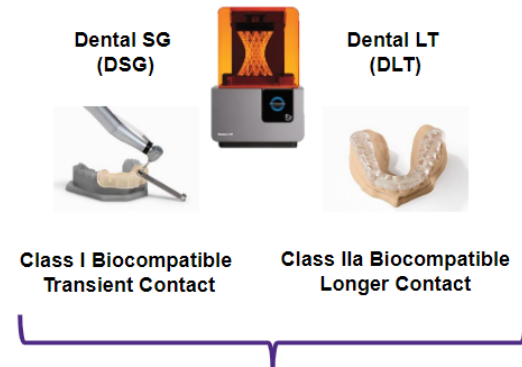
- **EVATAR**

- Revolutionary integrated microfluidic platform
- Expensive
- Not user friendly



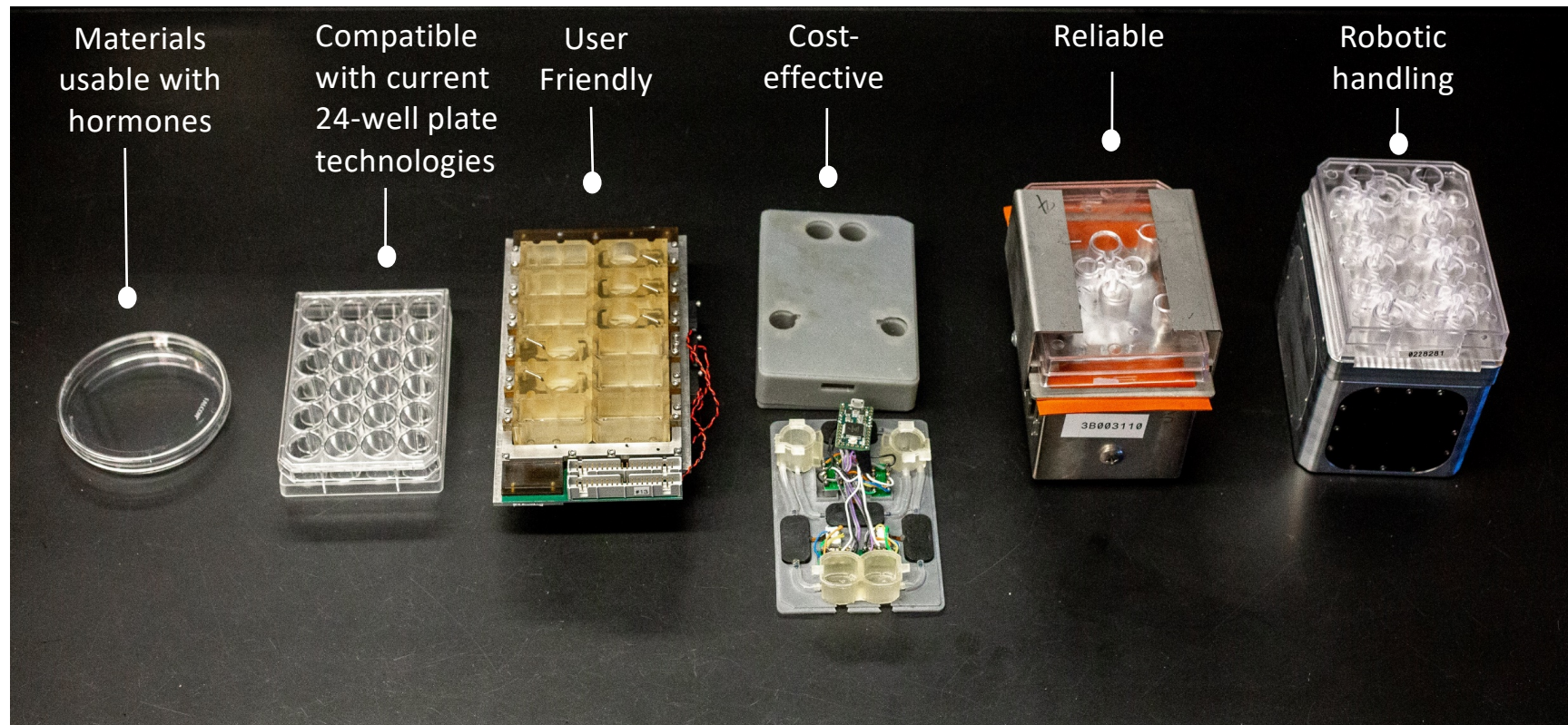
- **Blac tie**

- 3D printed MF system using the concepts of EVATAR in a familiar form factor.



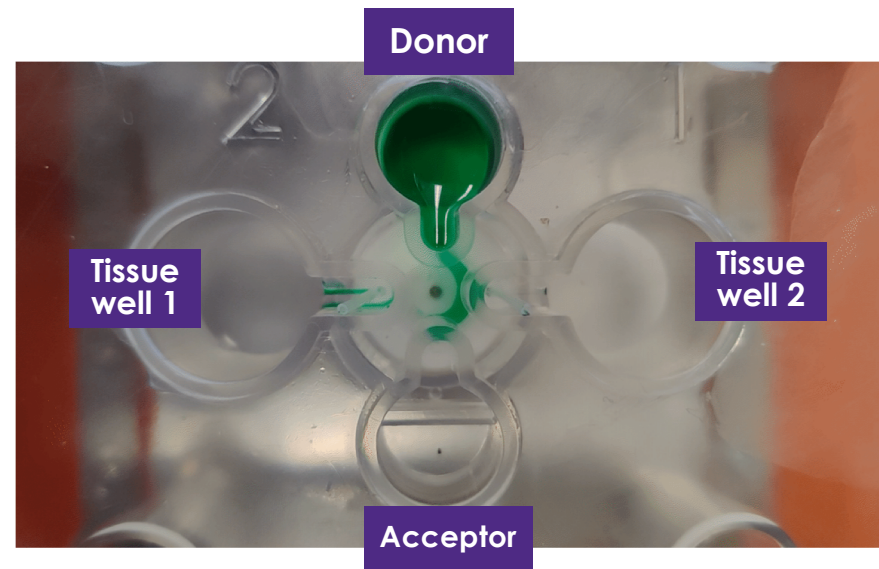
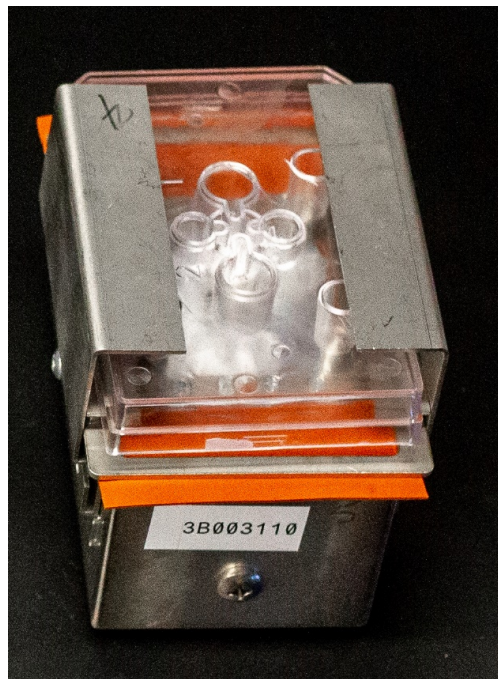
"Mixture of (meth)acrylated monomers, (meth)acrylated oligomers, and photoinitiators"

# Evolution from EVATAR to LATTICE

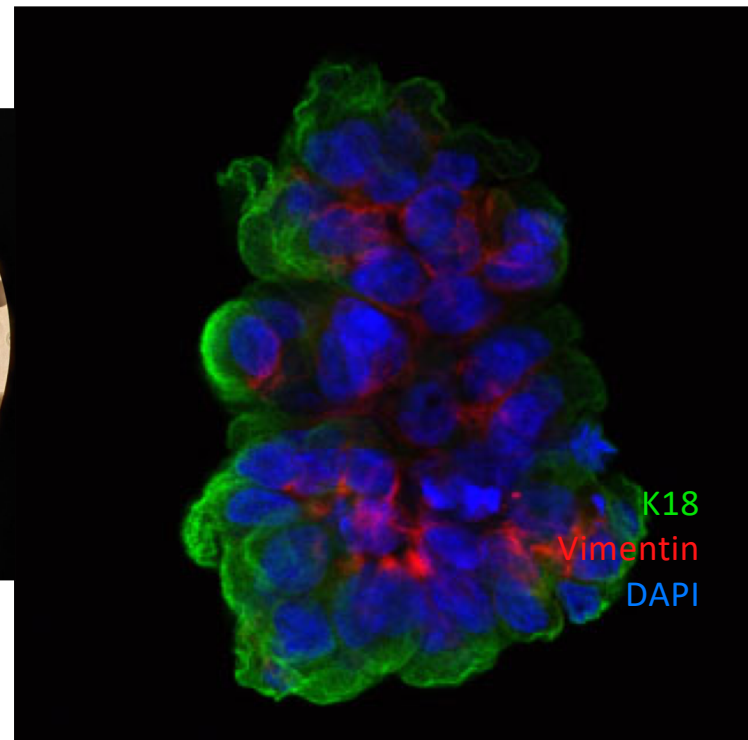
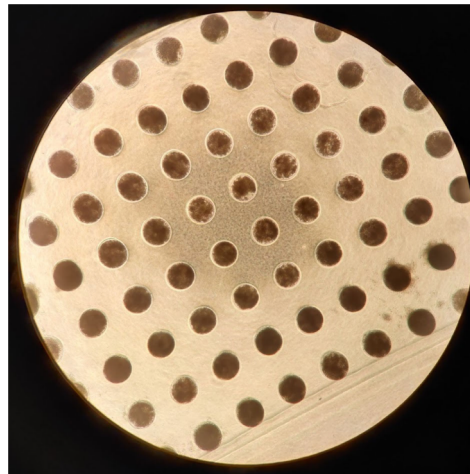
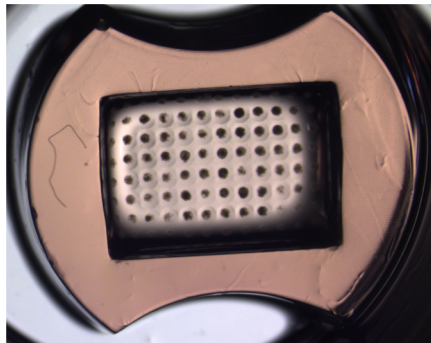
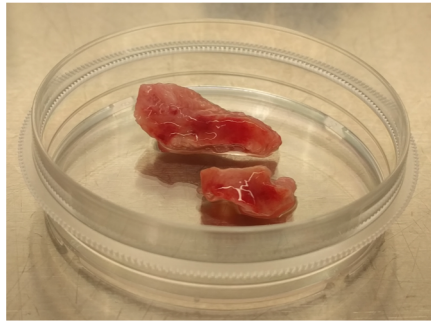




# Mechanics of 2 Organ Interaction on LATTICE



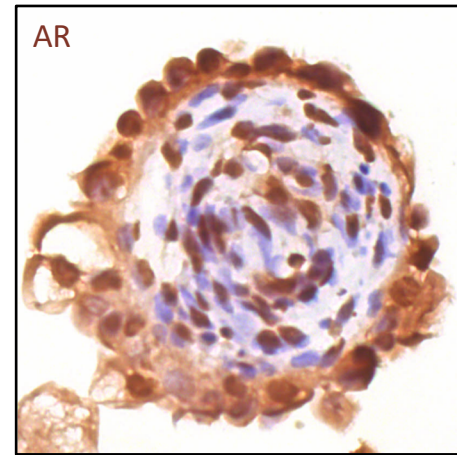
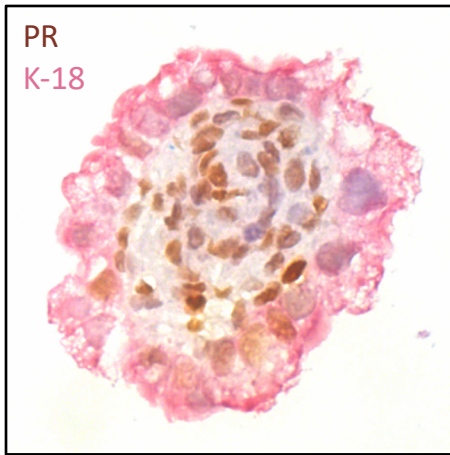
# Endometrial complex organoids on LATTICE



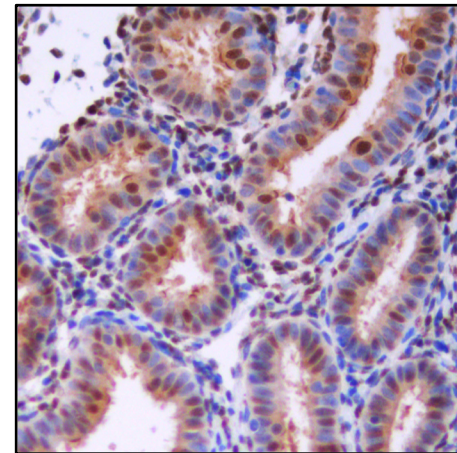
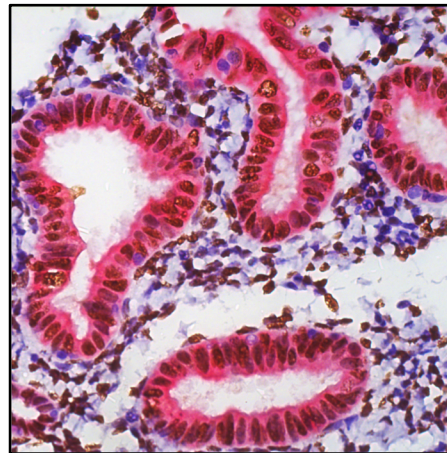
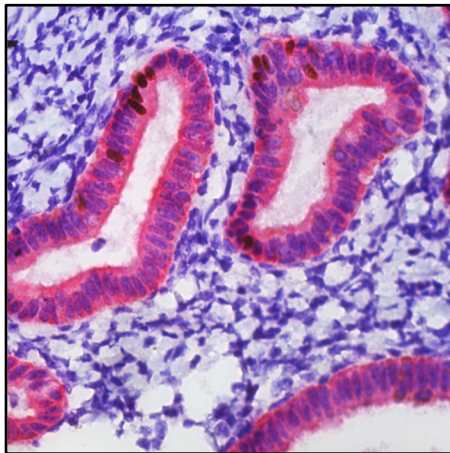


# Endometrial organoids express hormone receptors

Endometrial  
organoids



Endometrium



Endometrial  
cancer is  
elevated in  
PCOS and  
correlates  
with obesity

**Polycystic Ovary Syndrome:  
A Significant Risk Factor for  
Premenopausal Endometrial Cancer**



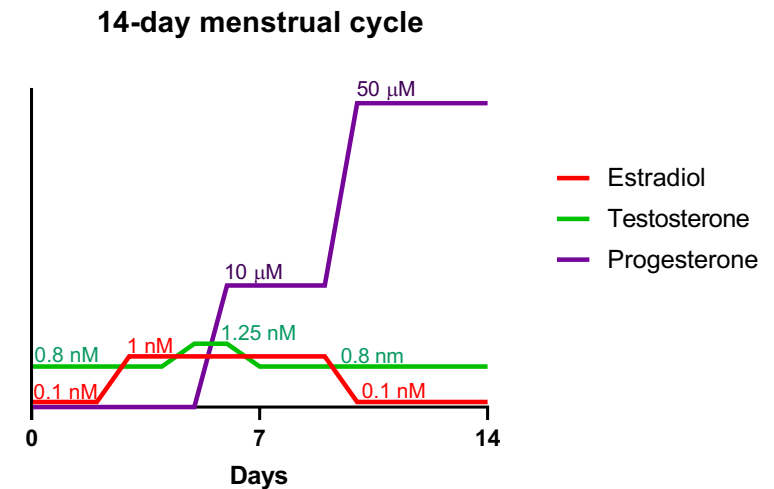
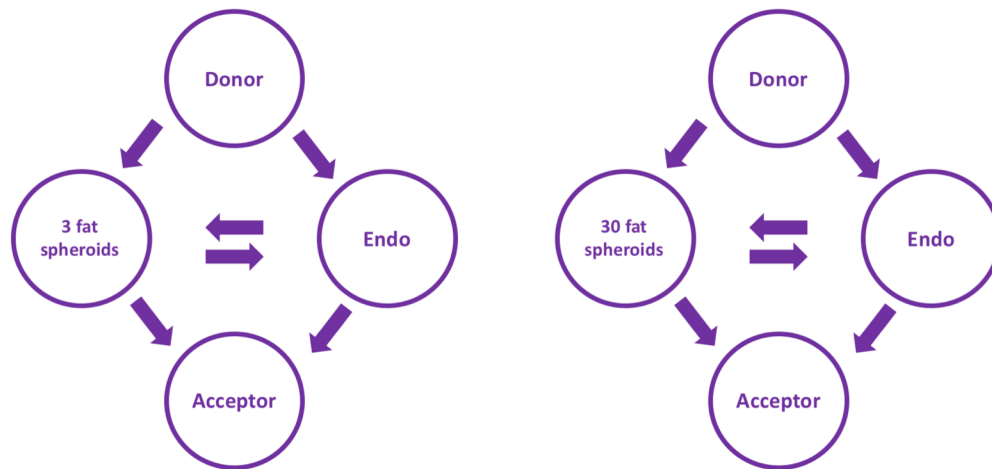
Women with PCOS and Endometrial Cancer more often:

- Have higher BMI
- Are insulin resistant
- Have not been pregnant
- Have irregular or absent cycles
- Diagnosed at more advanced disease stages
- Are resistant to usual EC medication (it doesn't work)
- Get hysterectomies compared to other EC patients without PCOS



[PCOSChallenge.org](http://PCOSChallenge.org)

# Dynamic coculture of endometrial organoids and adipocyte spheroids





# PCOS may play a role in fallopian tube function and cancer

Human Reproduction Update, Vol.20, No.5 pp. 748–758, 2014  
Advanced Access publication on March 30, 2014 doi:10.1093/humupd/dmu012

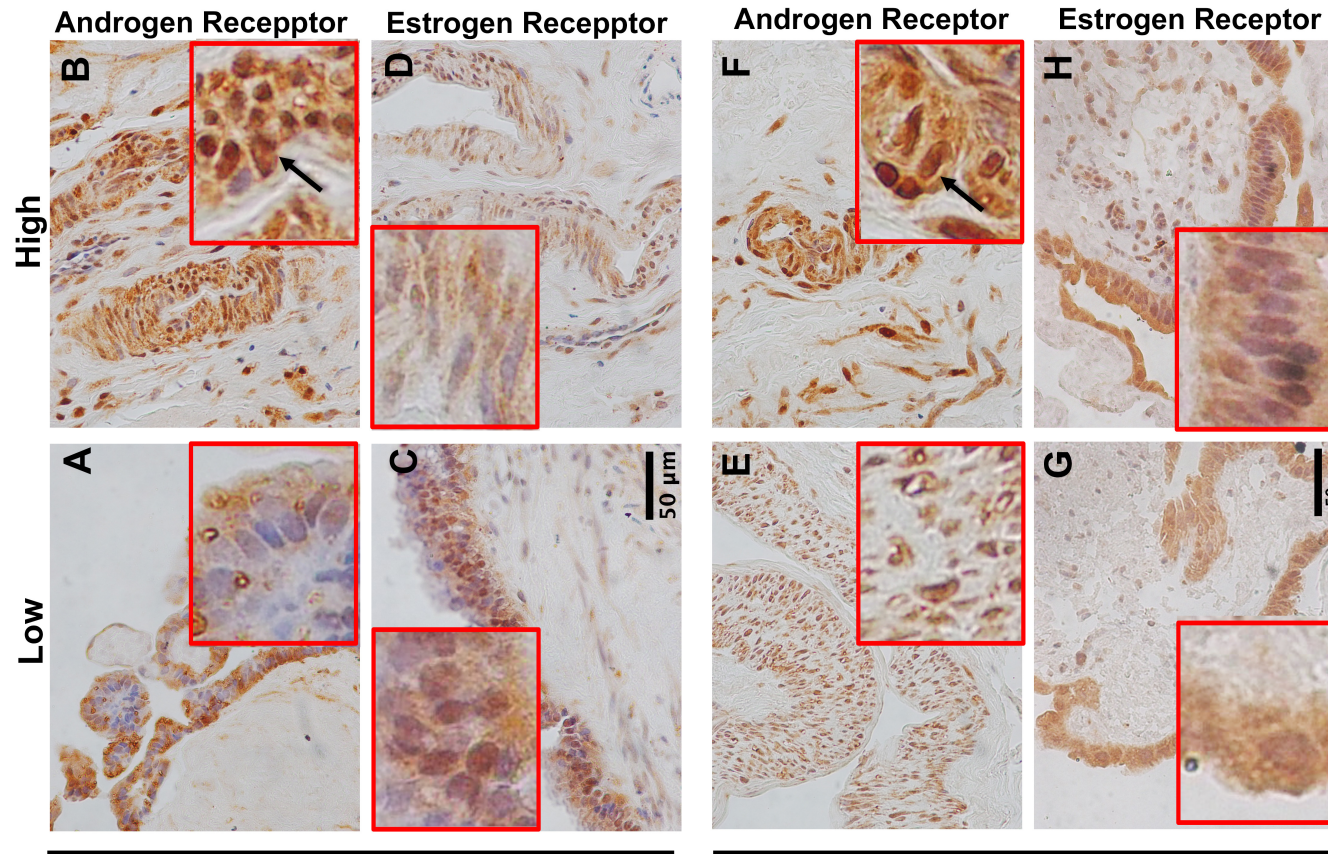
human  
reproduction  
update

## Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: a systematic review and meta-analysis

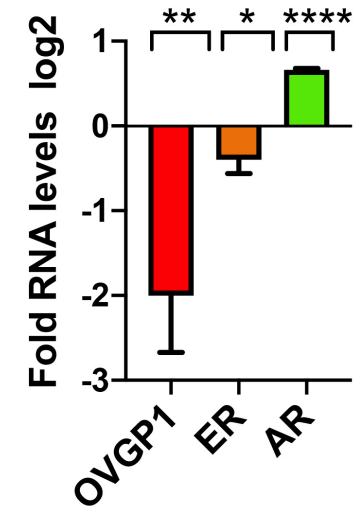
John A. Barry, Mallika M. Azizia, and Paul J. Hardiman\*

- When women aged over 54 years were excluded, the risk for women with became significantly increased for ovarian cancer (OR, 2.52; 95% CI, 1.08–5.89, P , 0.03)
- Testosterone has been shown to be associated with ovarian cancer risk.
- High grade serous ovarian cancer comes from the fallopian tube.

# Androgen exposure activates AR but blocks ER



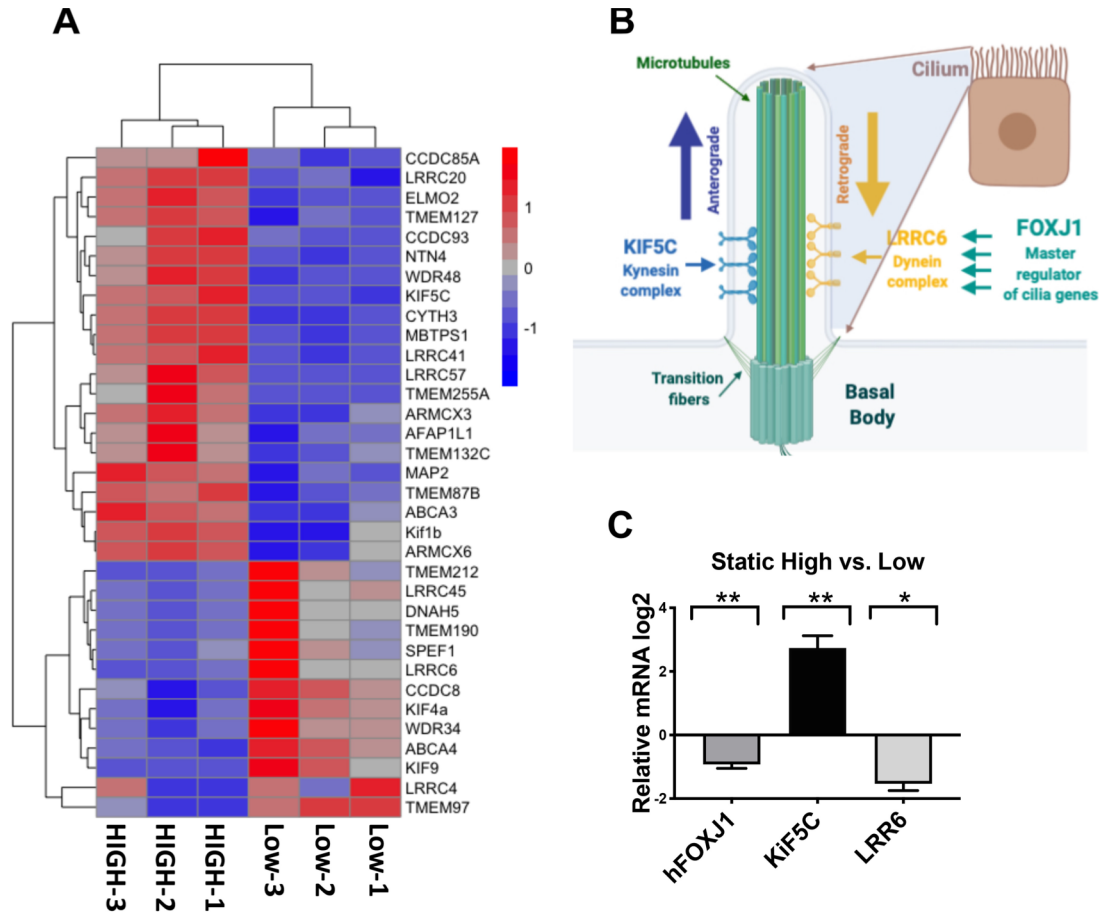
Static High vs. Low



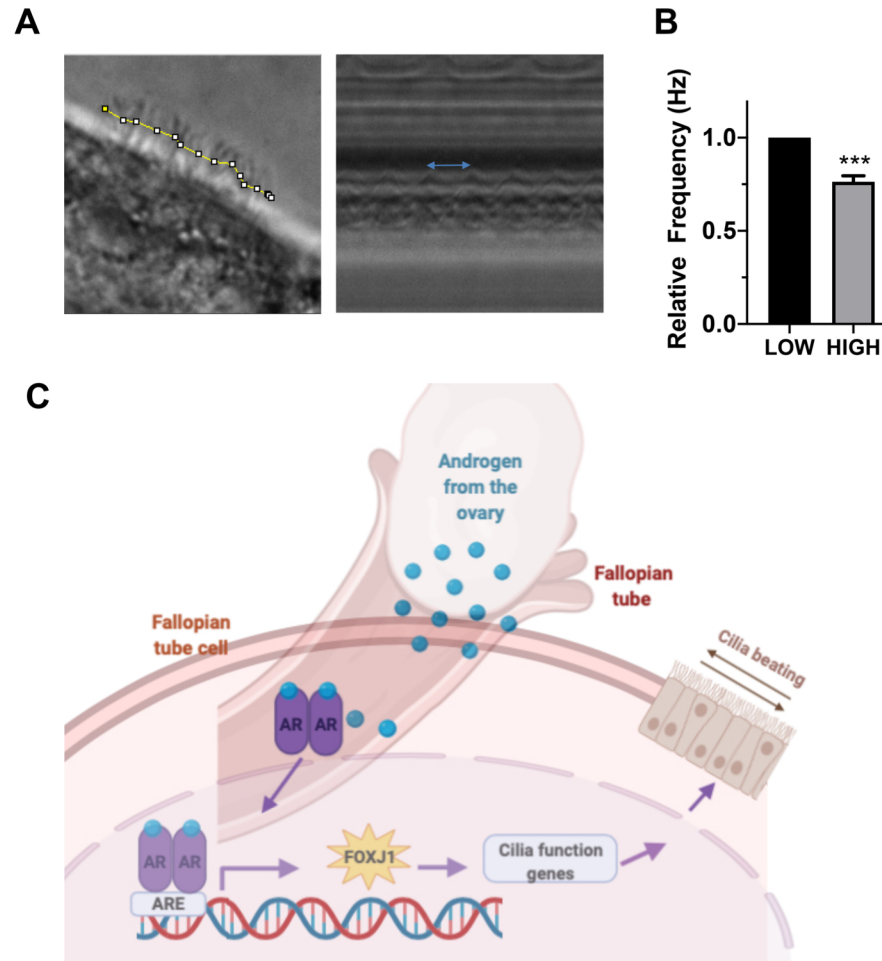
Static

Microfluidic

# Androgen represses genes encoding for cilia

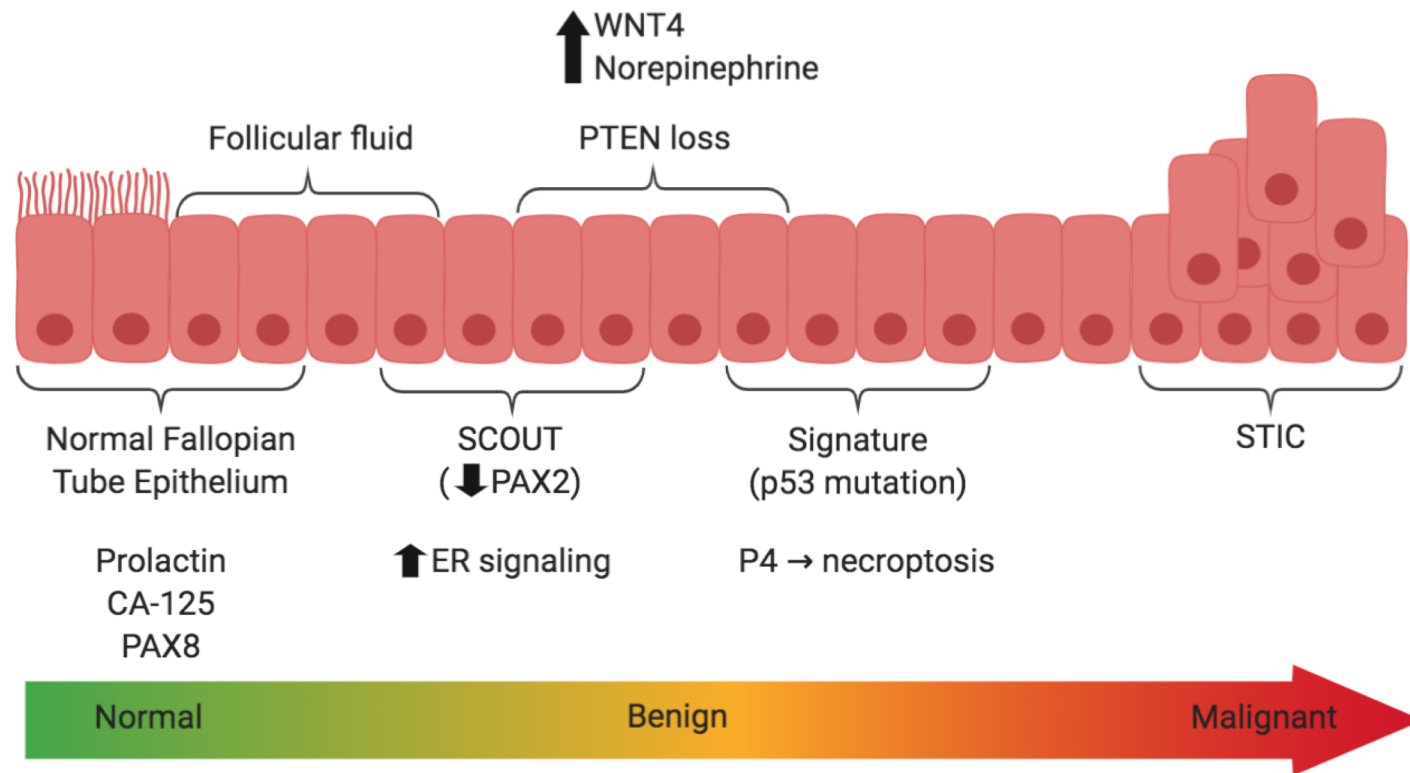


# Androgen reduces cilia beating frequency



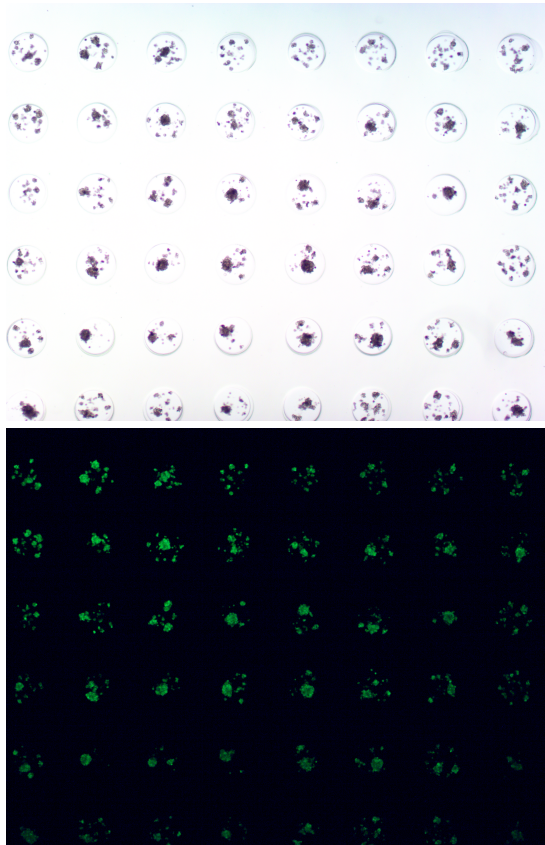


# Fallopian tube gives rise to high grade serous ovarian cancer

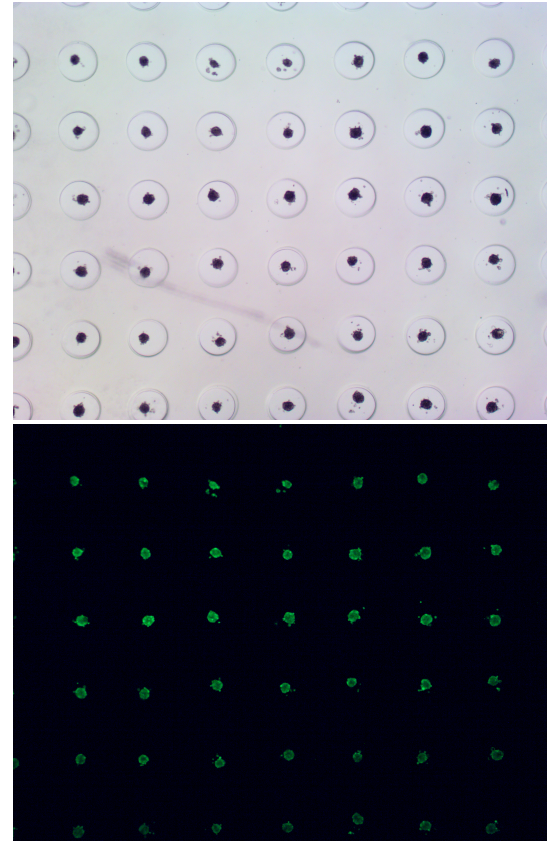


# Fallopian tube cell aggregates maintain circularity in microfluidic conditions

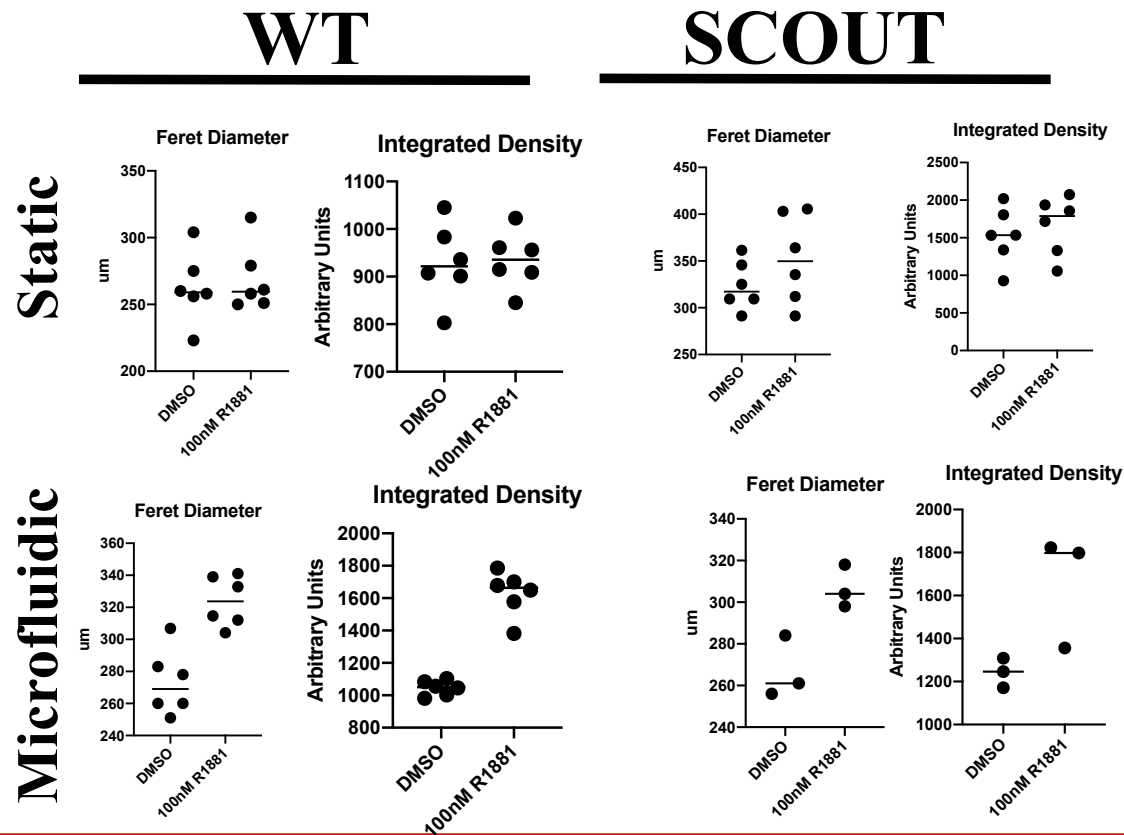
Static



Microfluidic



# Androgens induce proliferation in fallopian tube on a microfluidic device



R1881 = synthetic androgen

# Environmental chemicals may affect the pathogenesis and/or presentation of PCOS

- **In animal models** (Zhou et al. 2008, Alonso-Madgalena et al. 2006, etc. ):
  - BPA enhances ovarian androgen production *in vitro* perinatal exposure to BPA disrupts ovarian and reproductive function in females
  - BPA induces insulin resistance *in vivo* BPA also appears to have obesogenic properties
- **In humans** (Kandaraki et al. 2011, Hu et al. 2017, Takeuchi et al. 2004, etc.):
  - cross-sectional data suggests that BPA concentrations are higher in women with PCOS than in reproductively healthy women
  - androgen levels and BPA levels show a statistically significant relationship



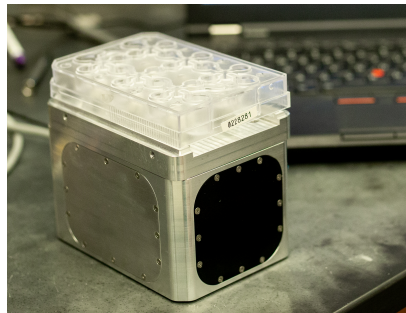


# Integration of up to 8 organ systems

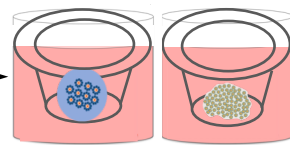


# Screening of Endocrine Disrupting

Lattice



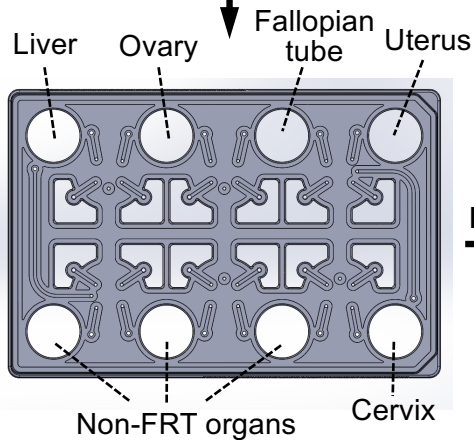
Ovary-on-a-chip



Normal ovaries

PCOS ovaries

- Follicle development
- Hormone secretion
- Ovulation

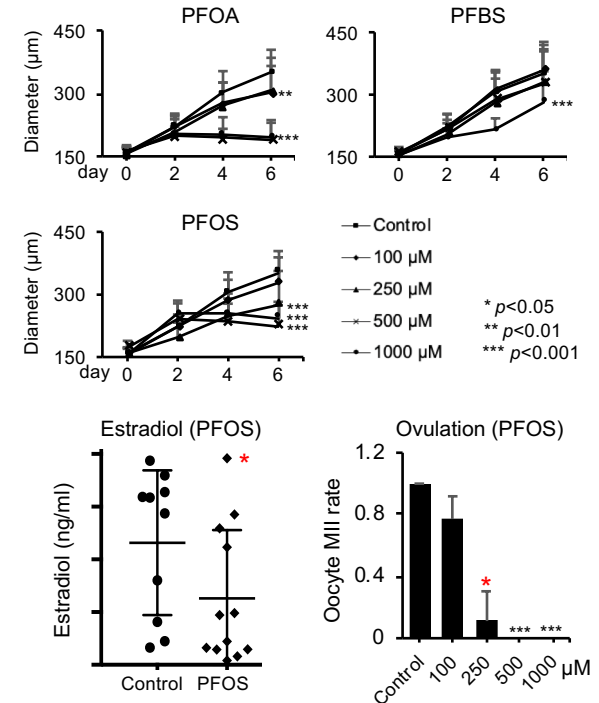


FRT-on-a-chip

## To to screened EDCs

- Bisphenol A (BPA) and BPA substitutes
- Phthalates (DEHP, DEP, DNOP)
- Phytoestrogens (genistein)
- Perfluorinated alkylated substances (PFAS)
- Dioxins (TCDD, PCBs)
- Brominated flam retardants
- Emerging environmental contaminants (HAB toxins)

## Screening of PFAS



# ACKNOWLEDGEMENTS

## UH3 Team

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