



# Oncofertility: From Bench to Bedside to Babies

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Northwestern University Feinberg School of Medicine



NIH

*Eunice Kennedy Shriver National Institute  
of Child Health and Human Development*

*Health research throughout the lifespan*

# Preservation of Fertility After Cancer

- Life preserving treatments
  - Chemotherapy
  - Radiation
  - Surgery
- **Can threaten fertility**



Jeruss & Woodruff **N Engl J Med** 2009;  
Woodruff **Nature Medicine** 2009;  
Woodruff **Nature Rev Clin Oncol**, 2010;  
Woodruff, **Nature Rev Endocrinol**, 2013;  
DeVos, Smitz, & Woodruff, **Lancet**, 2014;  
Gradishar, Smith, & Woodruff, **JAMA Oncol**, 2016



# the Oncofertility<sup>®</sup> Consortium

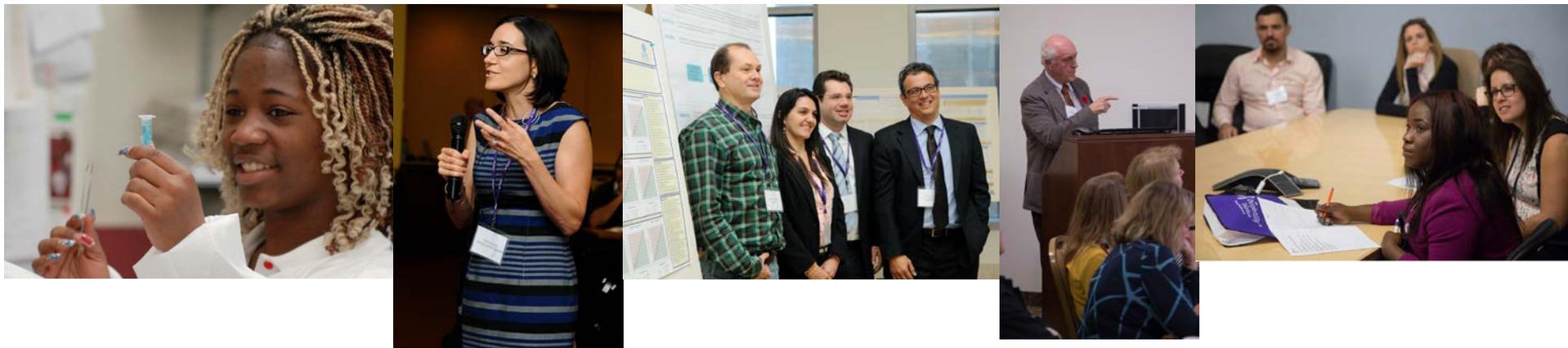
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the Oncofertility<sup>®</sup>  
Consortium

[www.oncofertility.northwestern.edu](http://www.oncofertility.northwestern.edu)

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NETWORK**



Funded by NICHD: P50HD076188



NORTHWESTERN UNIVERSITY  
**FEINBERG**  
SCHOOL OF MEDICINE



# National Physicians Cooperative

## An Infrastructure Partnering Medicine and Science



 **FERTLINE**  
866-708-FERT (3378)  
oncofertility@northwestern.edu

- 71 North America Sites
- 147 Sites Globally
- 19 Pediatric Sites



[oncofertility.northwestern.edu](http://oncofertility.northwestern.edu)

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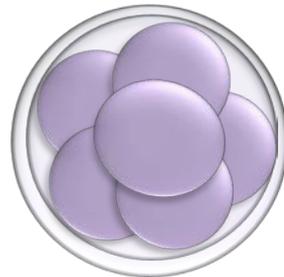
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NETWORK**

# Options for Women



**Egg Bank**



**Embryo Bank**

- Embryo/Egg Bank
- Adoption, Surrogacy
- Natural Pregnancy
- Ovarian Cryopreservation
  
- Fertility
- Endocrine Health
- Sexuality/Contraception

Jeruss & Woodruff **N Engl J Med** 2009; Woodruff **Nat Med** 2009;  
Woodruff **Nat Rev Clin Oncol**, 2010; Woodruff, **Nat Rev Endocrinol**, 2013;  
DeVos, Smitz, & Woodruff, **Lancet**, 2014; Gradishar, Smith, & Woodruff, **JAMA Oncol**, 2016

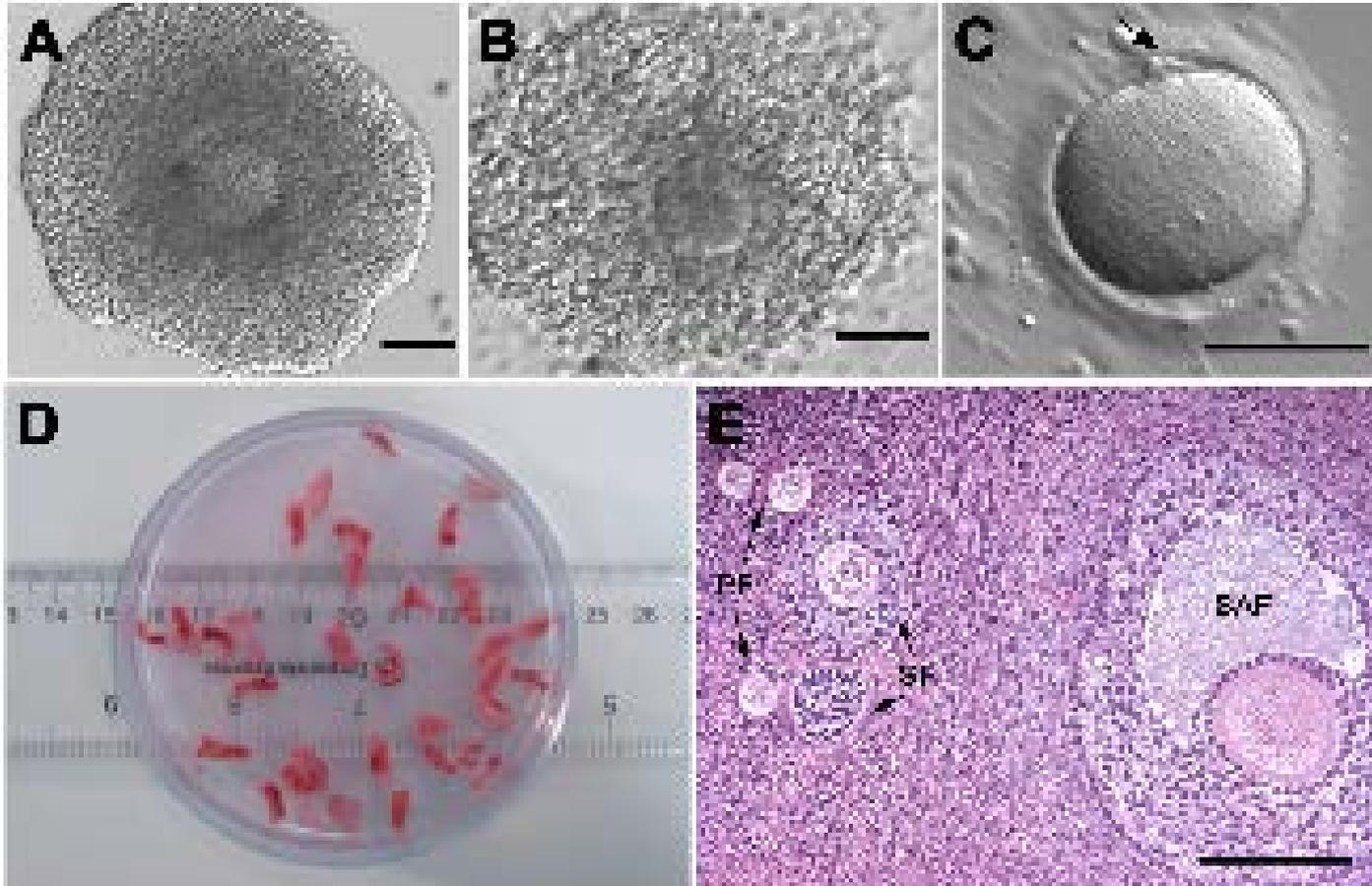
# Options for Women



- 12 day average wait
- Options and time available (even in hormone positive setting)
- Fertility intervention can improve non-initiation or non-compliance associated with tamoxifen treatment

Kong, Skory, Woodruff, Creating a continuum of care: Integrating obstetricians in the care of young cancer patients *Clin. Obstet Gynecol* 54:619 (2011); Llarena, Jeruss, *JNCI* 2015

# Tissue Cryopreservation for Patient Use and Research



Xu et al. *Human Reproduction*, 2009;  
Duncan et al, *Reproduction*, 2016

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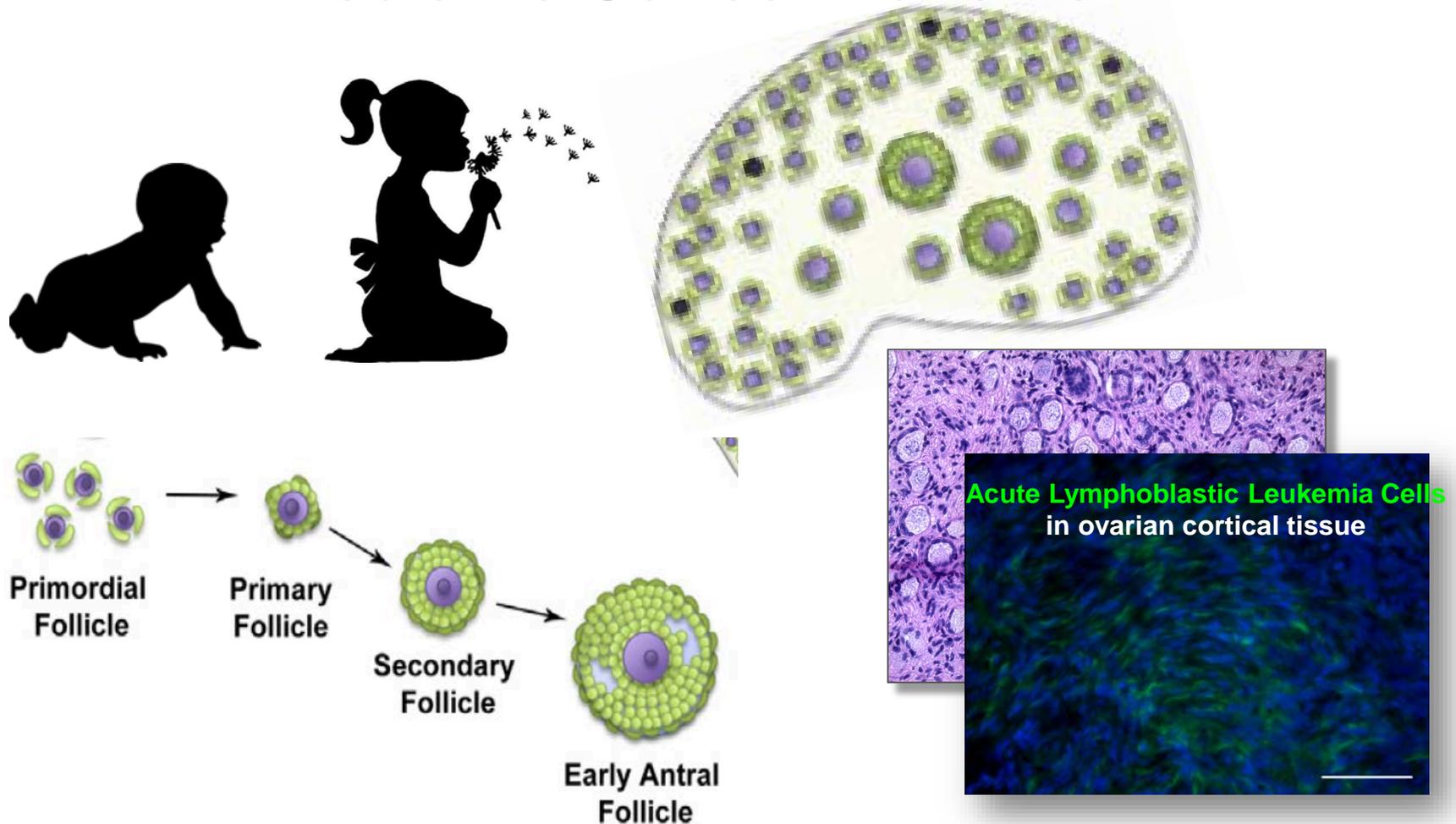
# Tissue Transplant: >86 Human Births



Sherman Silber, St. Louis;  
Donnez, Belgium; Suzuki, Japan

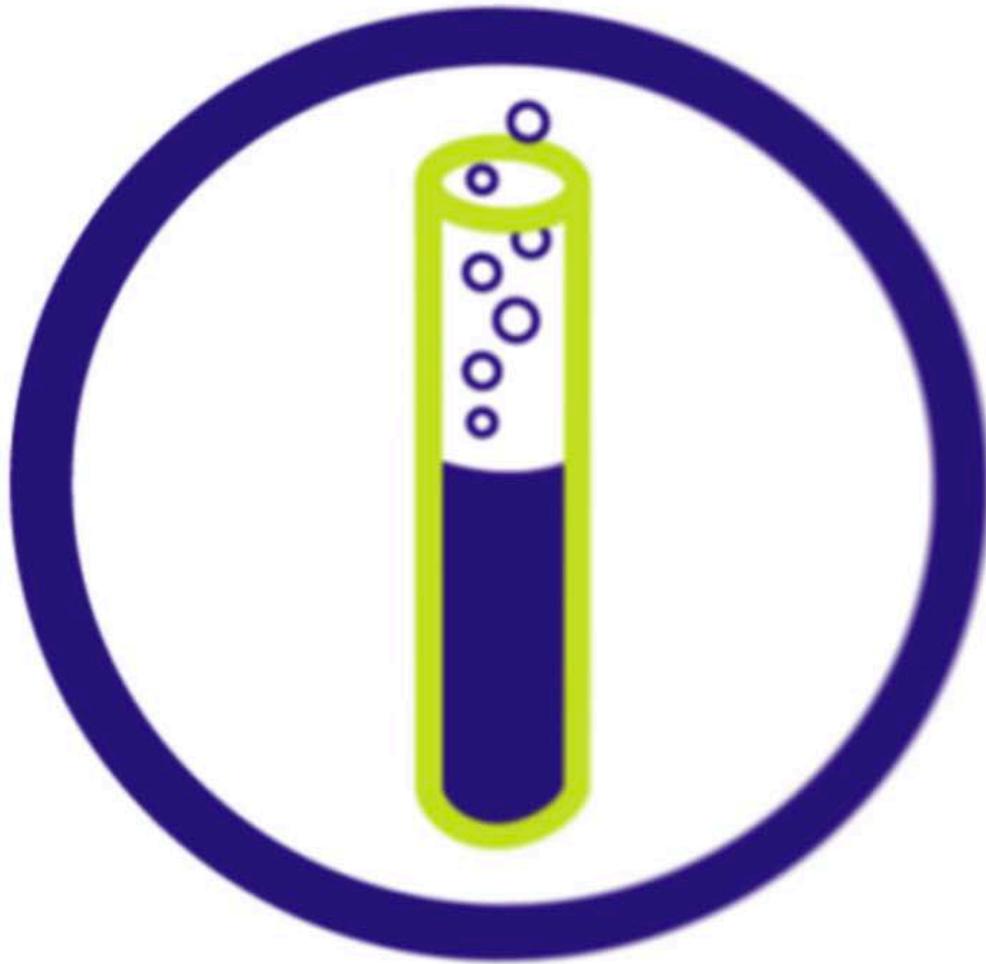
## Efficiency - Cancer Recurrence

# Fertility and Endocrine Needs of Pediatric Cancer Patients



Acute Lymphoblastic Leukemia Cells  
in ovarian cortical tissue

Figure in: Cordeiro, Kim, Woodruff. *Cancer Treatment and the Ovary* (2015)  
Patient Sample 4 y.o.; scale bar = 100  $\mu$ m; National Physicians Cooperative  
Laronda, et al. (2015) Biomaterials



# RESEARCH

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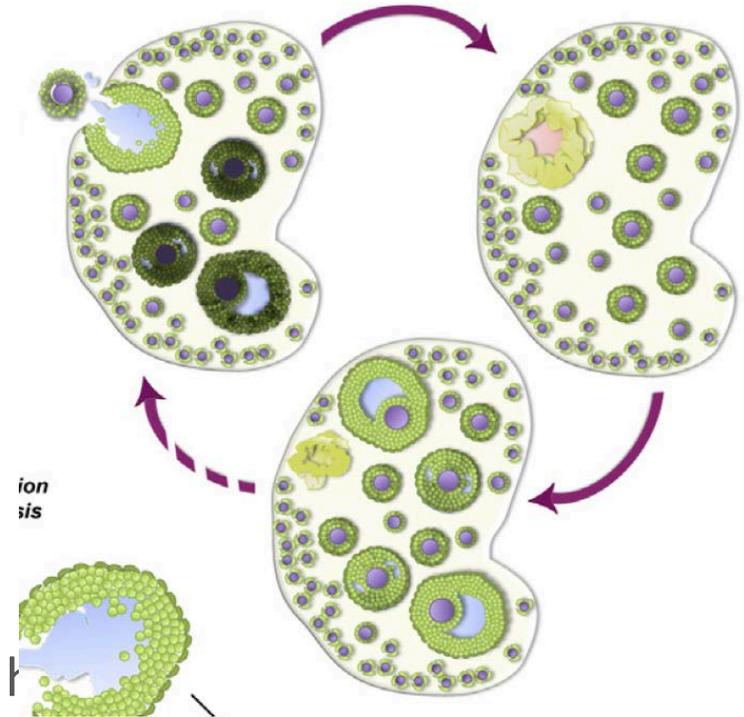
the  
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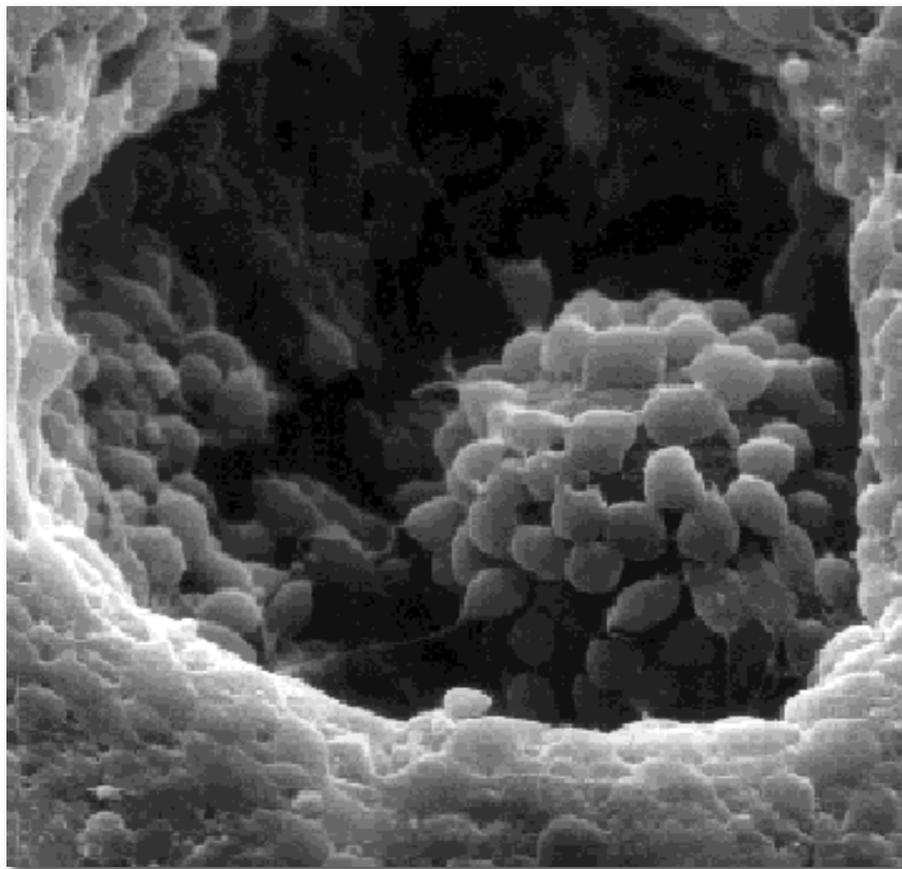
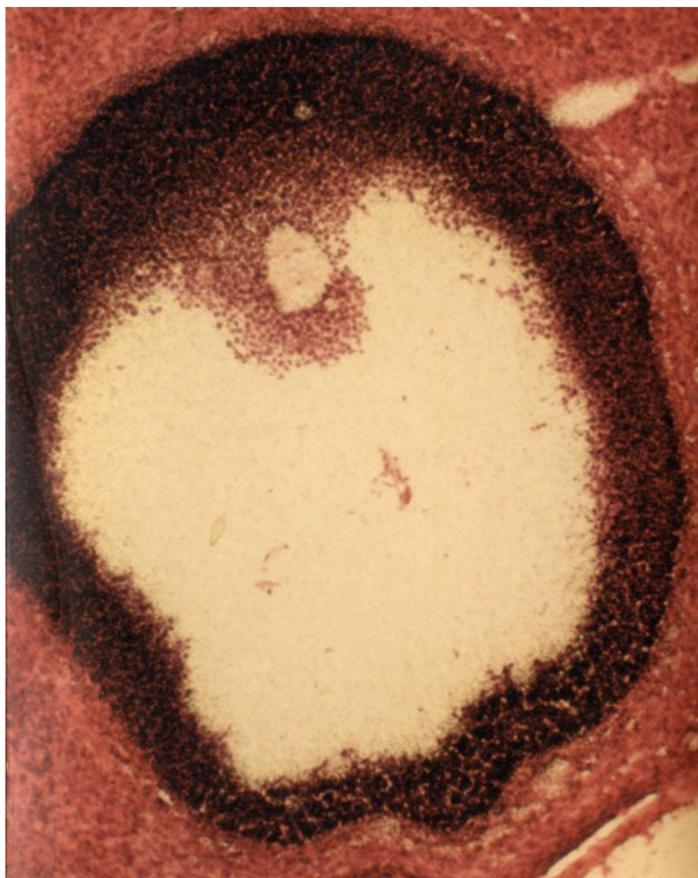
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# Fertility and Endocrine Needs of Pediatric Cancer Patients

- Follicle maturation
- High fidelity oocyte maturation
- Endocrine hormone production
- Pubertal transition
- Cyclical hormones to support systemic health



# Perhaps the structural context matters to developmental competence



Woodruff et al, *Science*, 1988

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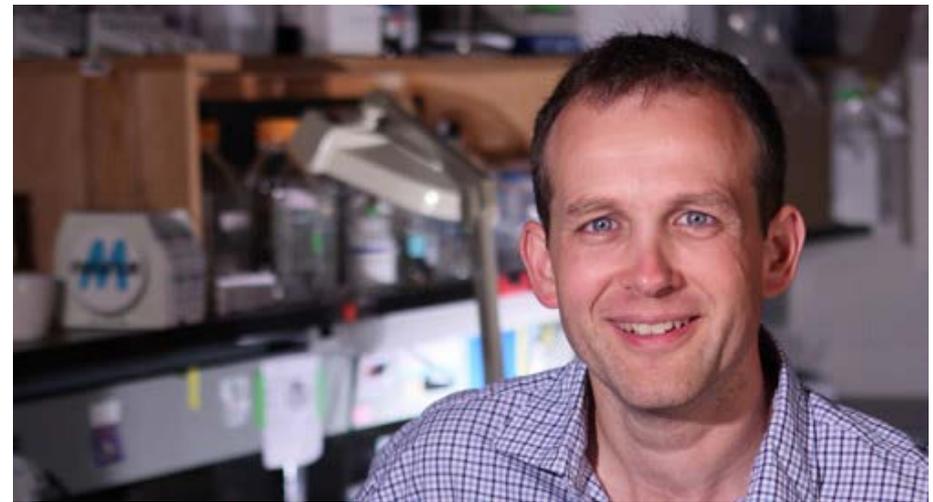
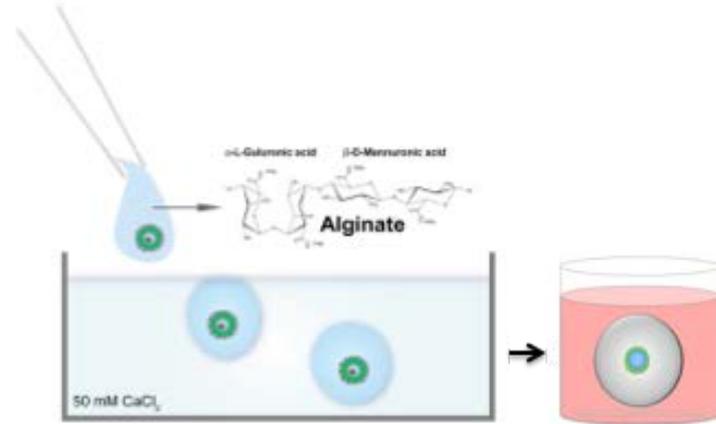
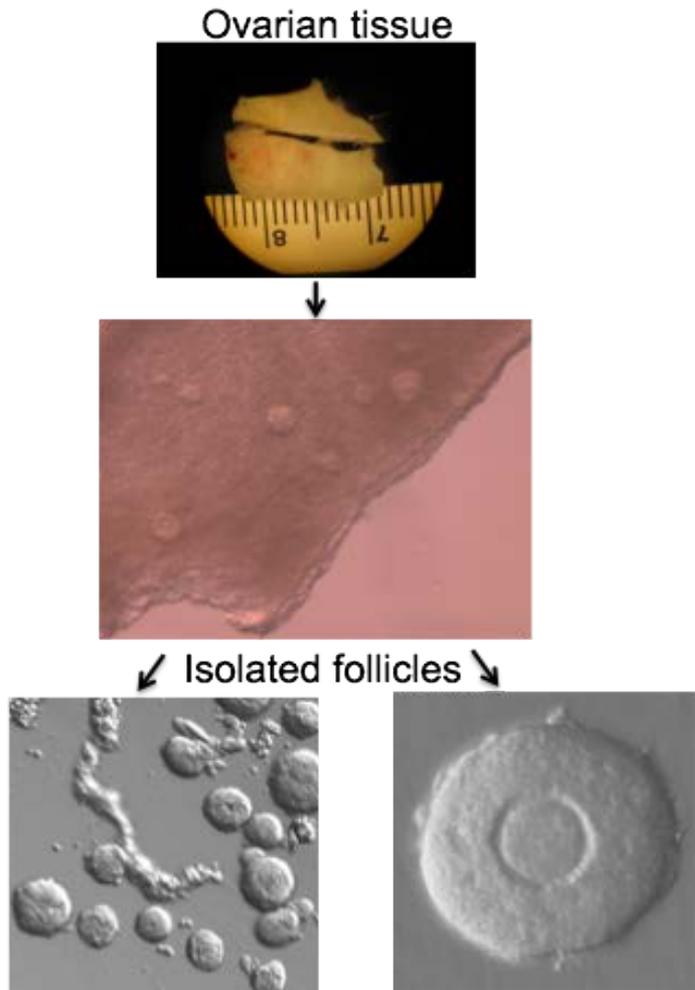
the  
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The Ribbon

# Encapsulated In Vitro Follicle Growth (eIVFG)

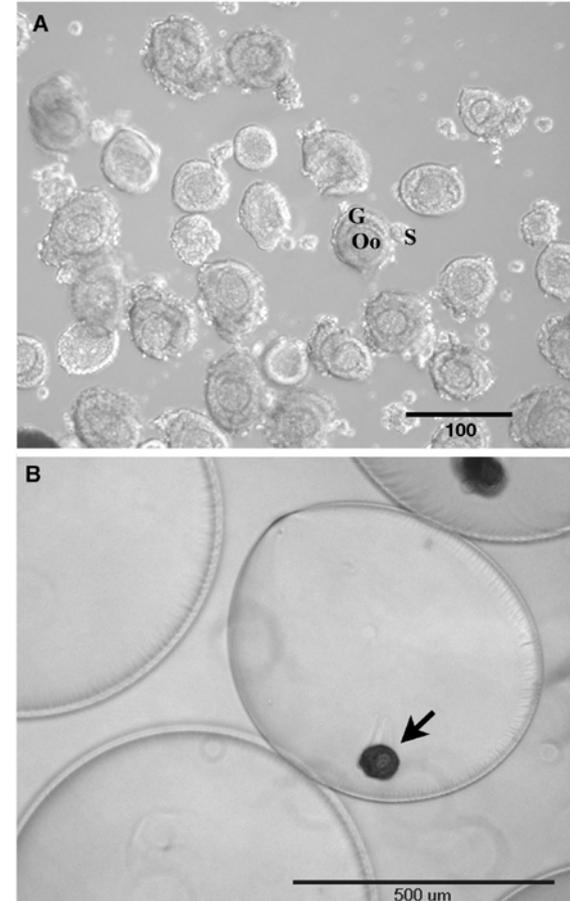


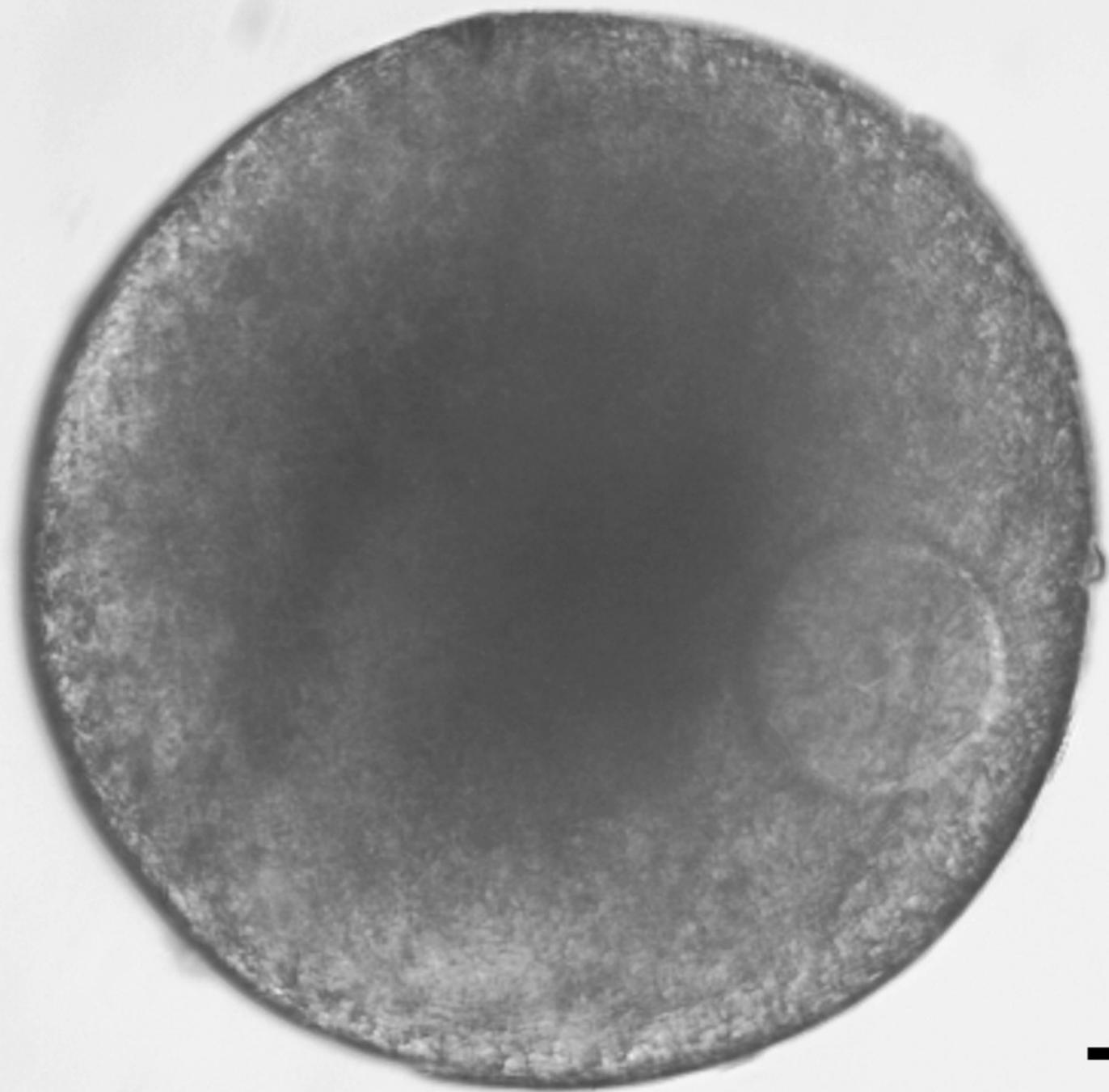
Lonnie Shea, Ph.D.

# Encapsulated In Vitro Follicle Growth (eIVFG)

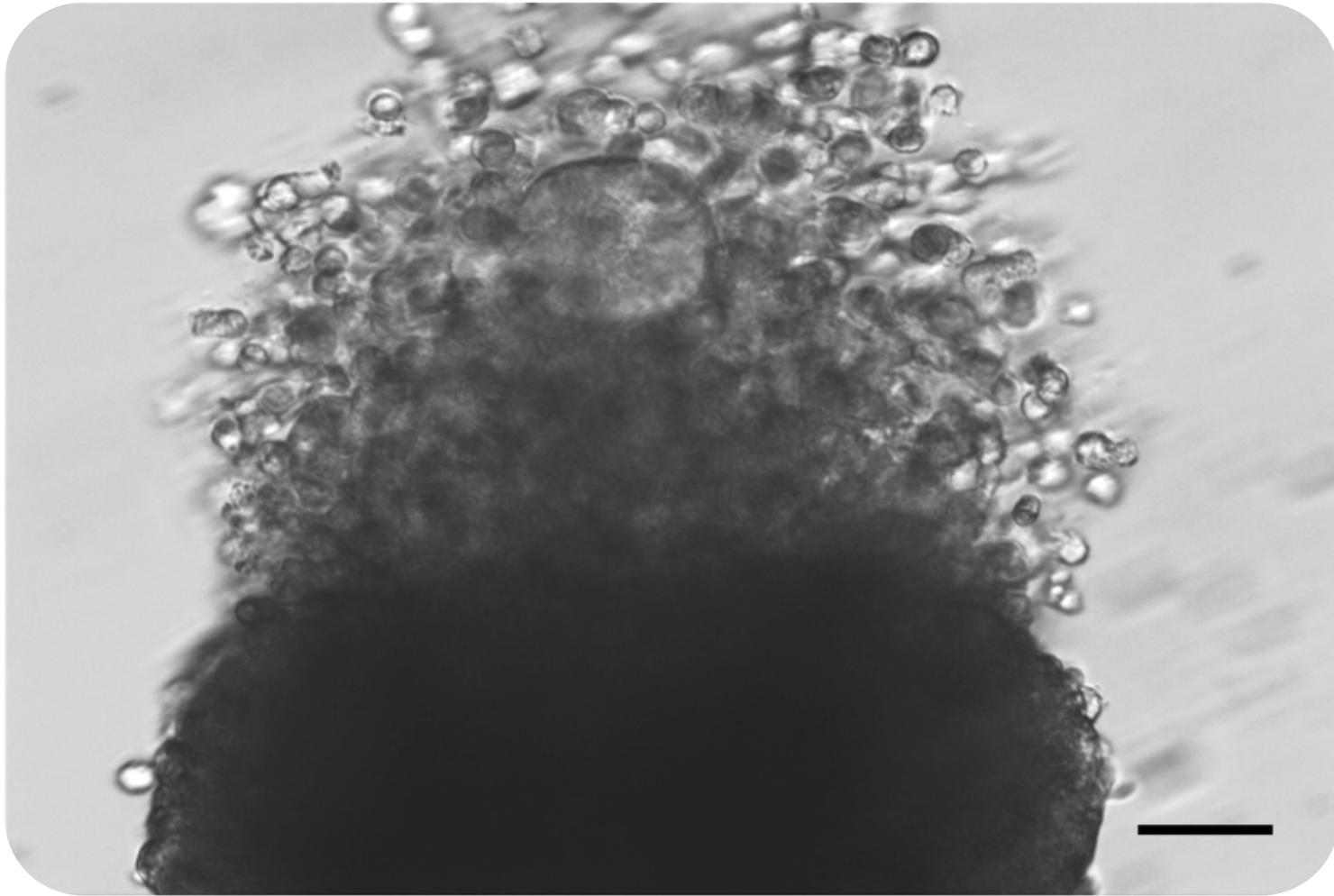


Successful Thesis Defense!





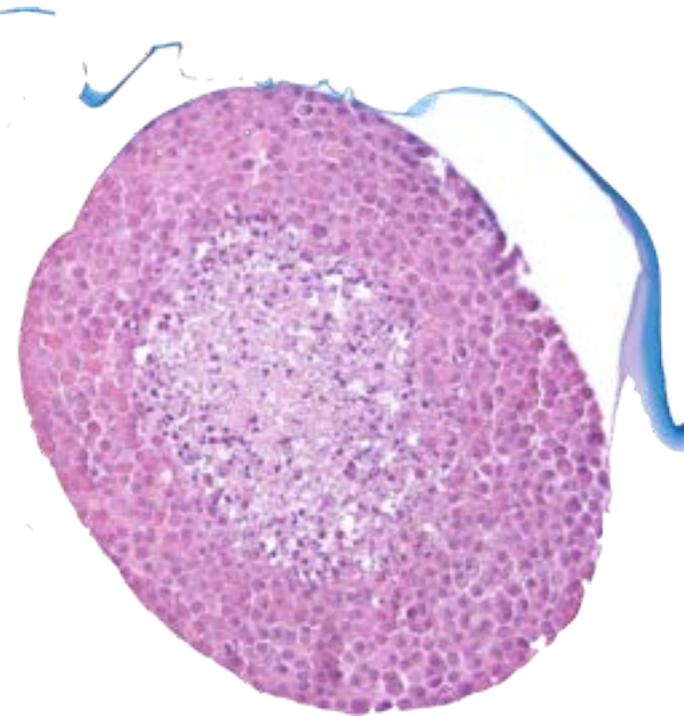
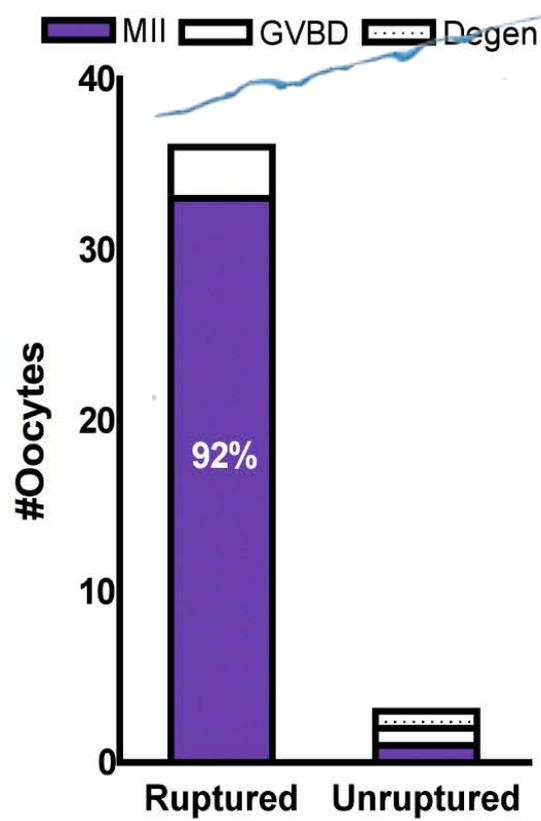
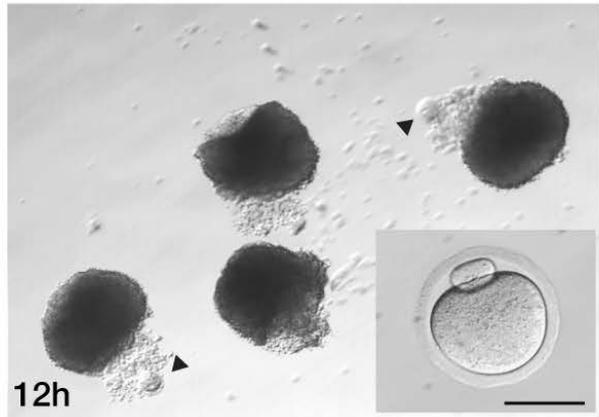
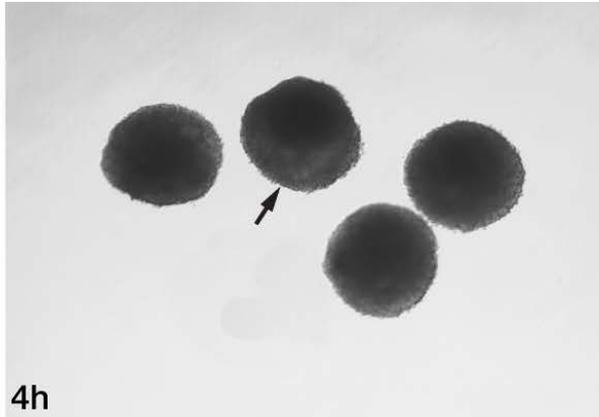
# In Vitro Ovulation



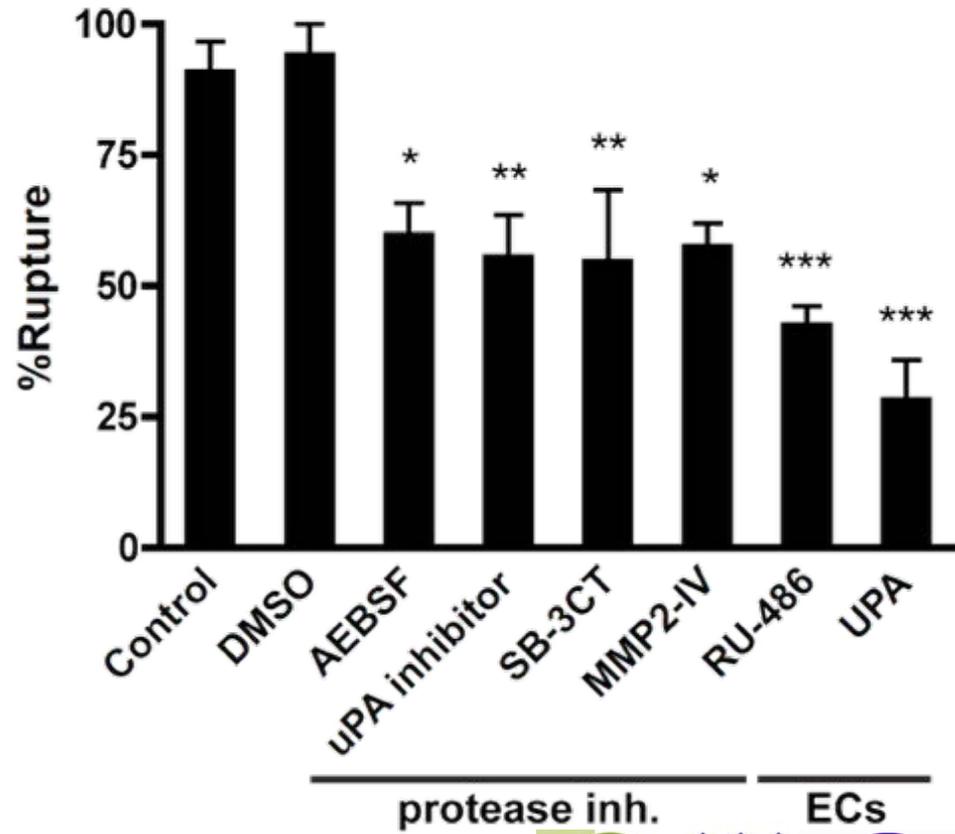
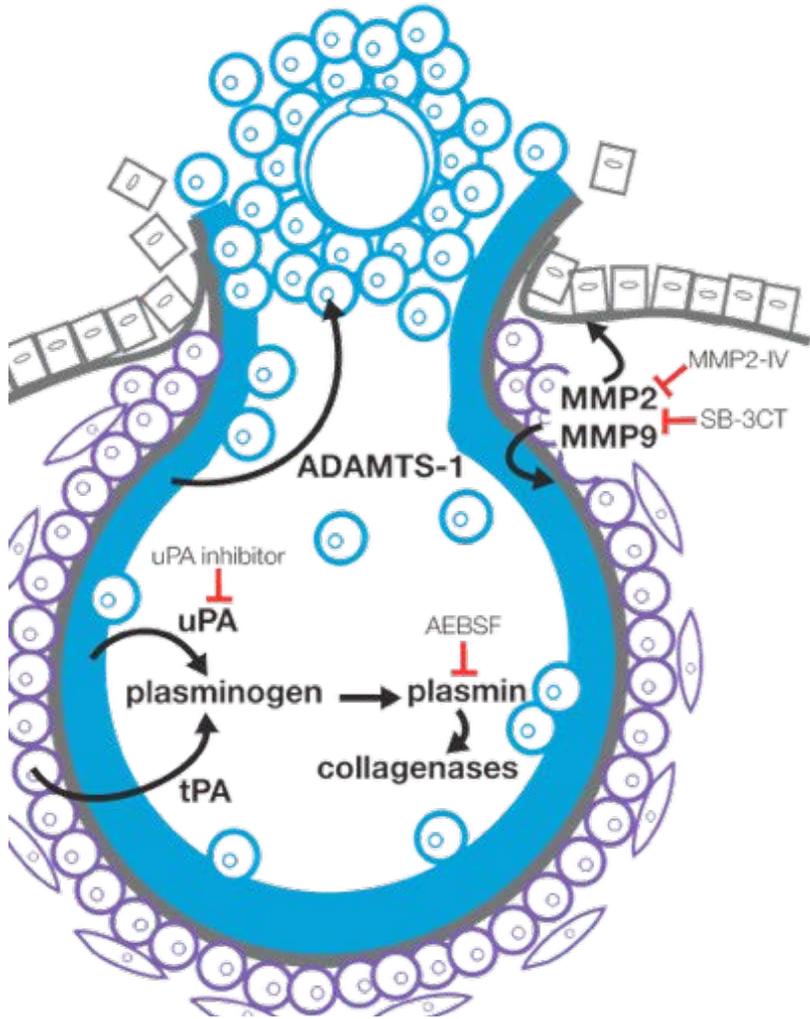
Skory, Xu, Shea and Woodruff, *Human Reprod.* 2015



# In Vitro Ovulation and Luteinization



# Mechanisms of Ovulation



Skory, Xu, Shea and Woodruff, *Human Reprod.* 2015;  
Gates Foundation



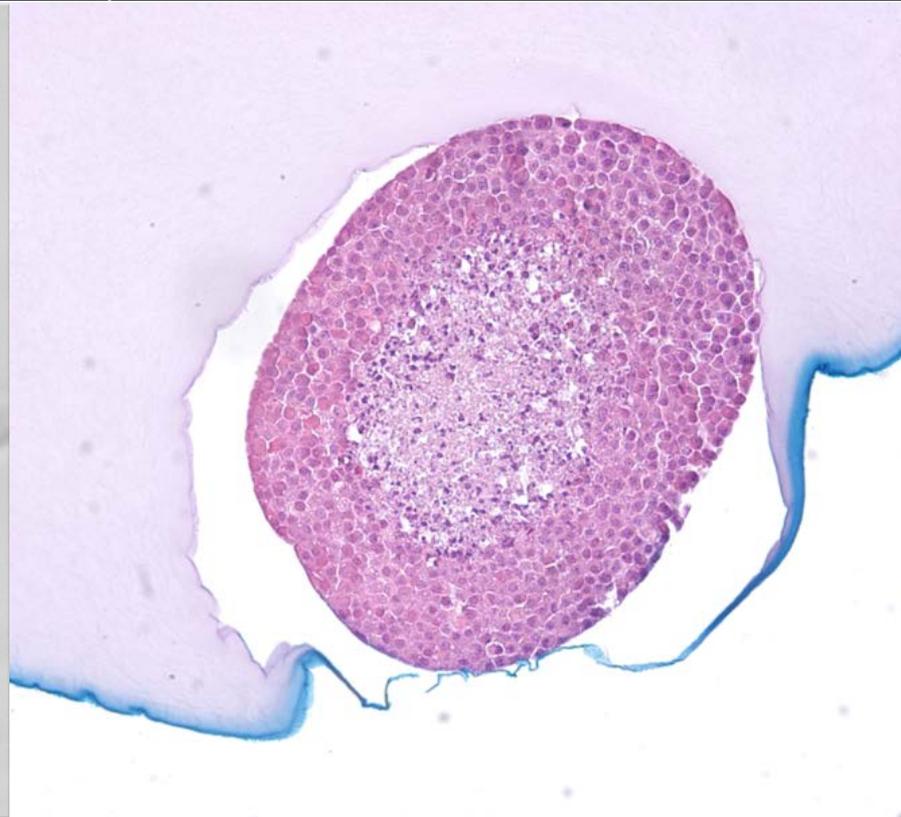
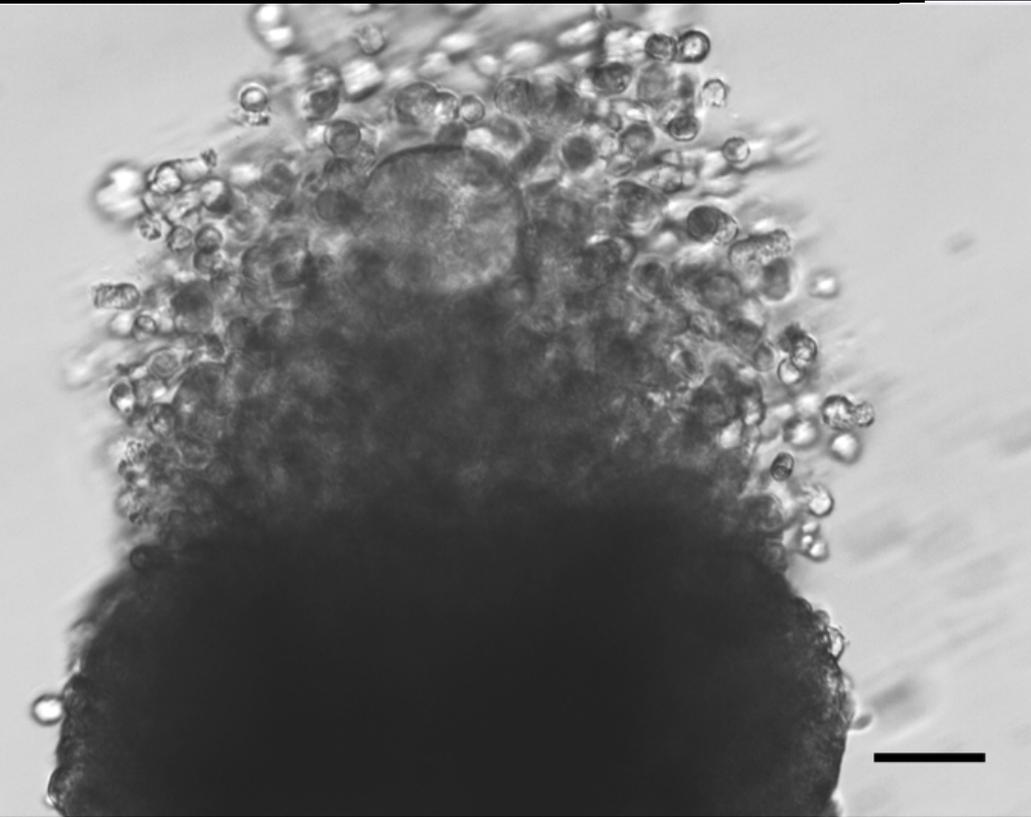
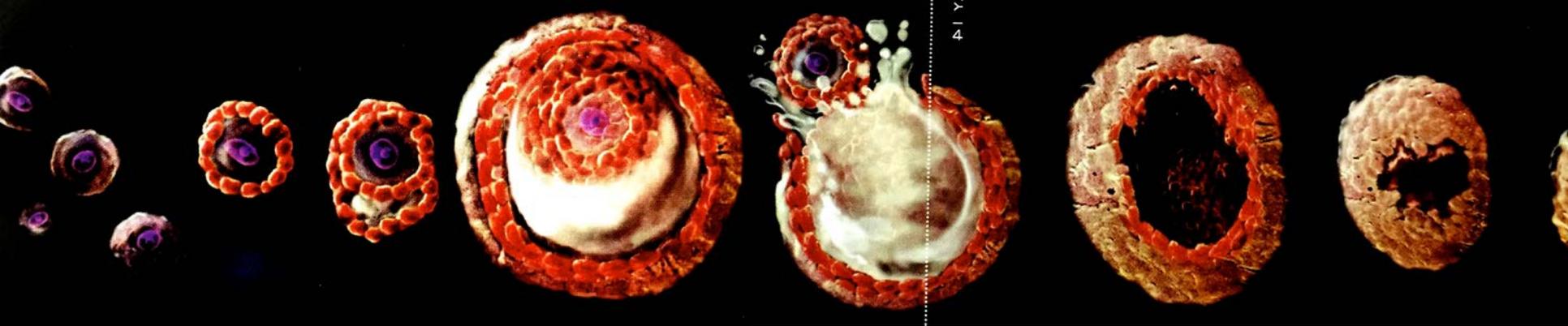
# eIVFG Produces MII Eggs and Supports Live Birth

nature medicine



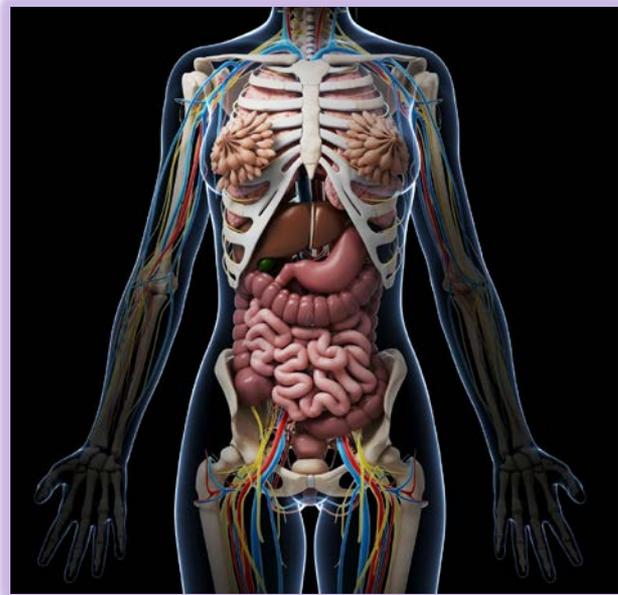
*Nature Medicine* Breakthrough of the Decade (1998-2008)





Funded by NICHD: P50HD076188

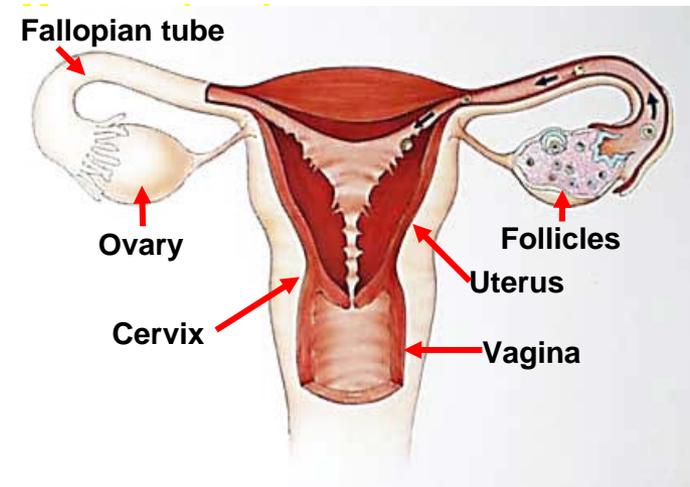
# How Do We Change Basic Discovery Research?



# Reproductive Tract Toolbox: *Earlier Discovery and Improved Safety*

- Contraceptive Design and Targets
- Environmental Health Toxin ID
- Vaccine Development
- Infectious Disease Drug Screening
- Cancer Drug Development
  
- Gestational Drug Development
  
- Early Development/Testing of Drugs
  - Reduce sex bias in pipeline
  - Precision approach to drug development
  - Increase safety of drugs for both sexes
  
- Sex Specific Drug Metabolism

Female Reproductive System



Kim, Woodruff, *Nature*. 2010

■ Woodruff, *PNAS* 2014

Eddie et al. *Experimental Biology and Medicine*, 2014

Laronda et al. *Stem Cell Research and Therapy*, 2014



# Microfluidic Follicle Culture



## Imaging

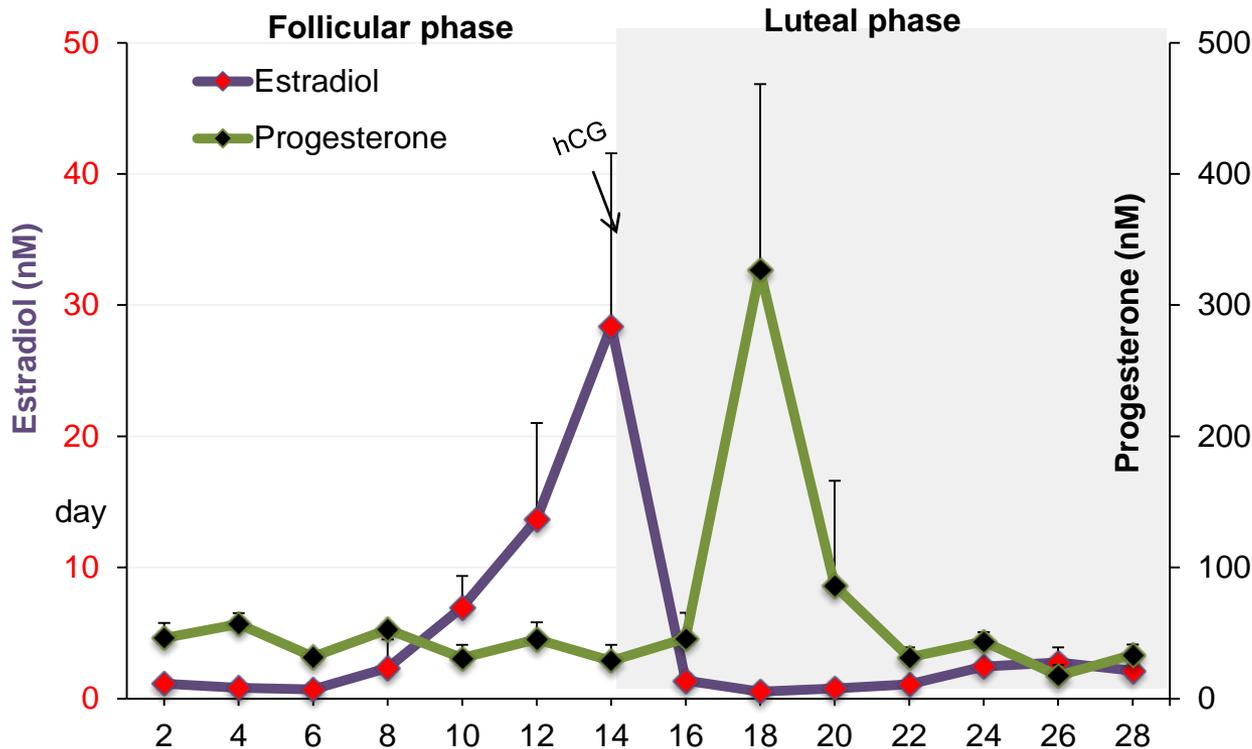
Funded by NIEHS/ORWH/NCATS/NICHHD

FemKube Image Integration: Mingyang Jiang  
Dino-Lite AM4815ZTL



FemKUBE: Engineering Reproductive Solutions

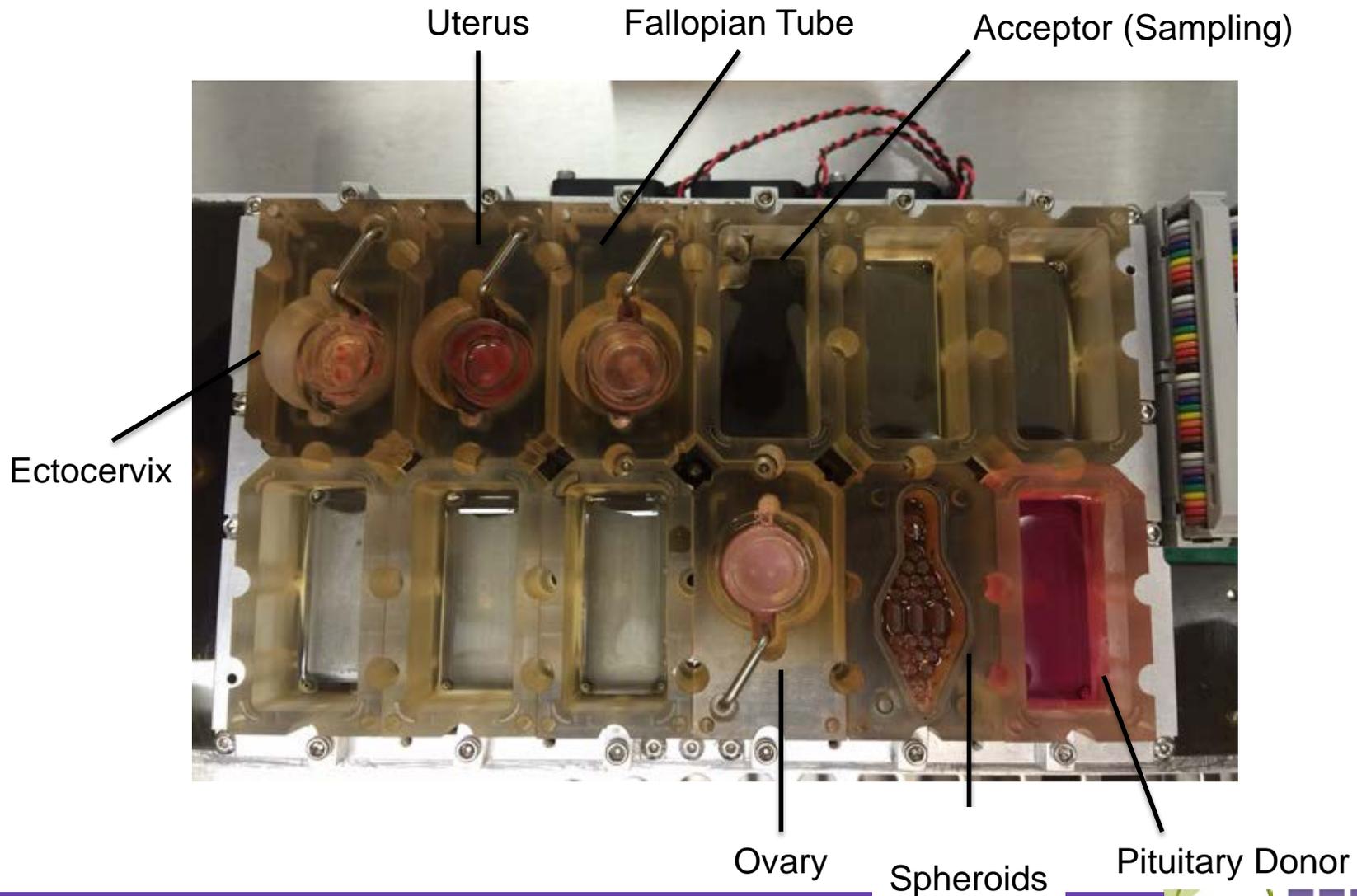
# Microfluidic Follicle Culture



4 complete 28 day experiments  
80 follicles per experiment  
Stable flow; hormone profiles

## Operator Training, Stable Flow, Sampling

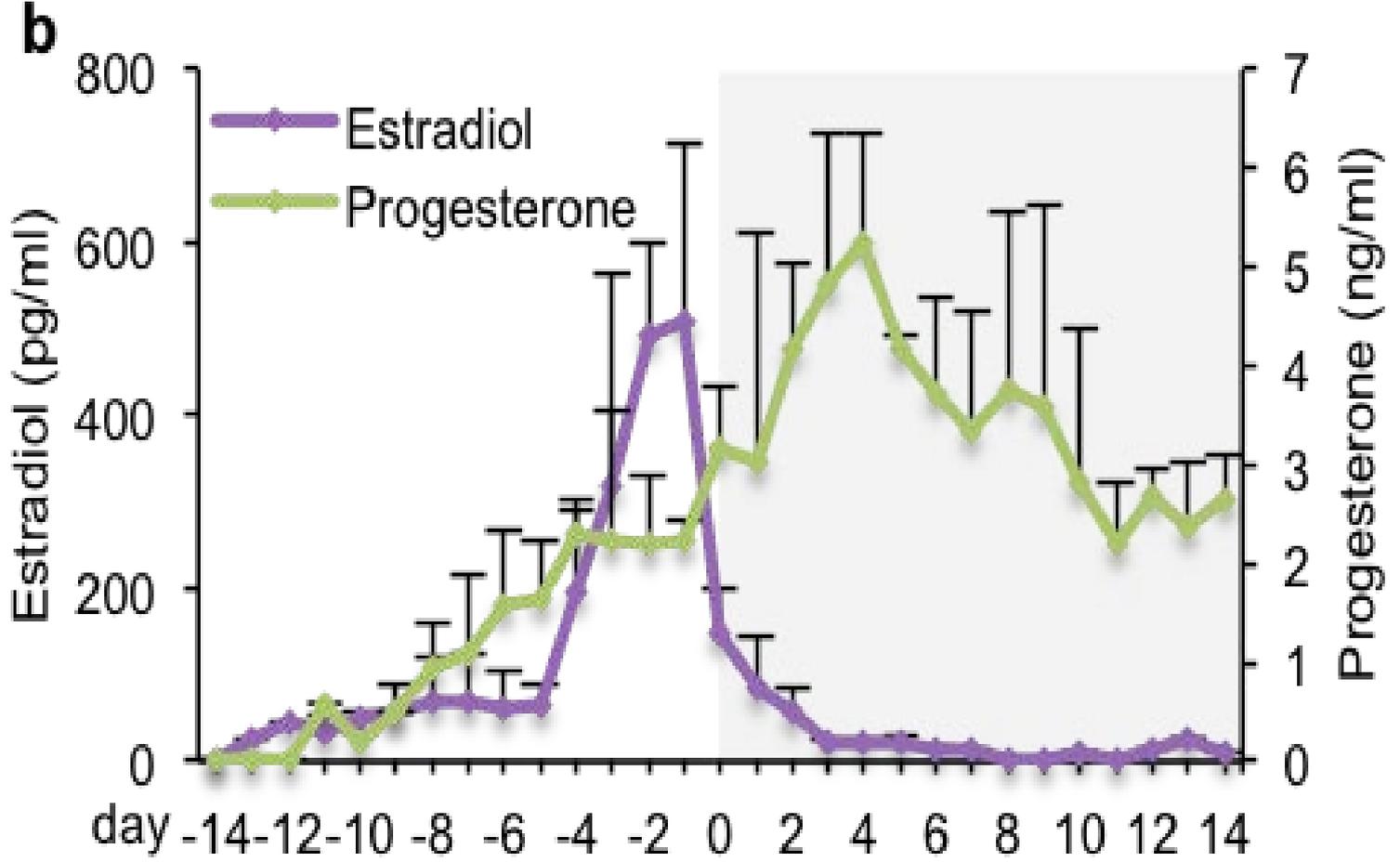
# EVATAR – Ovarian Cycle in a Dish



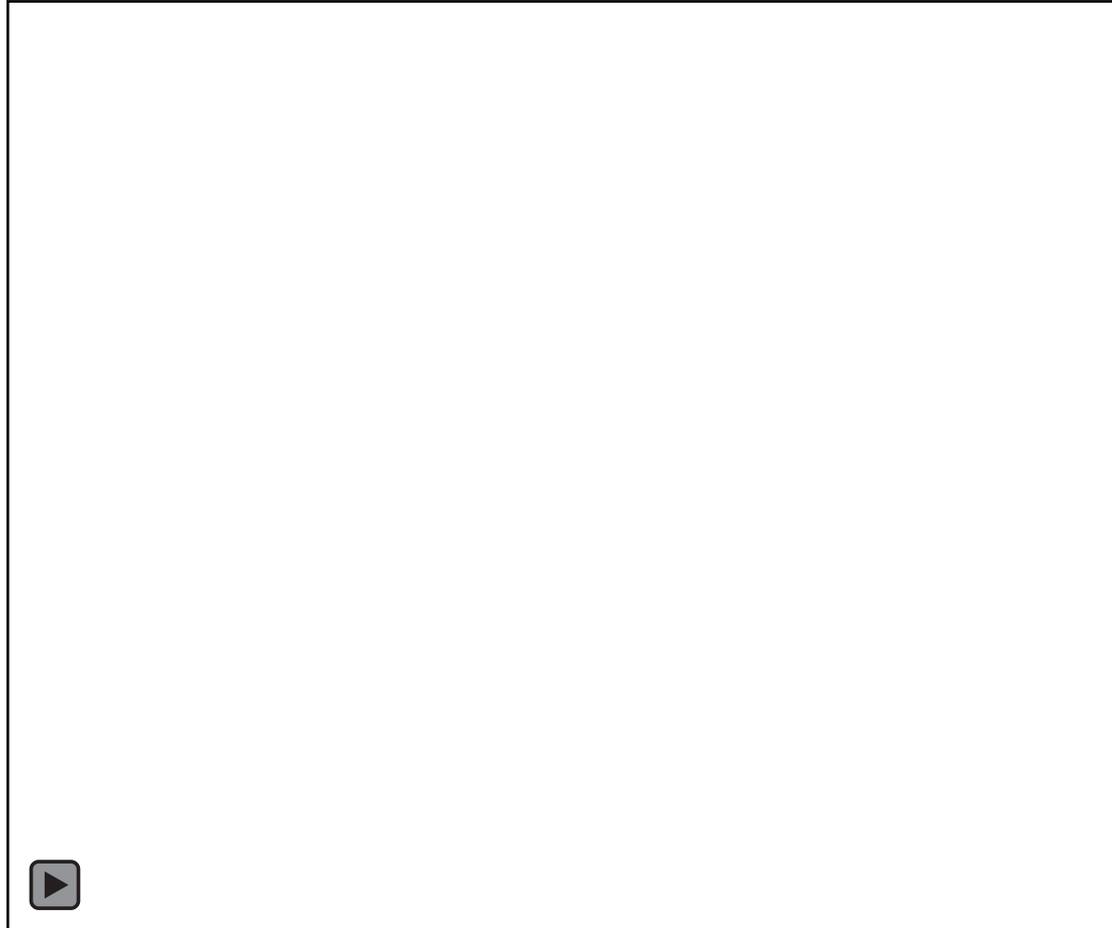
Xiao et al, *Nature Commun*, 2017.



# EVATAR™



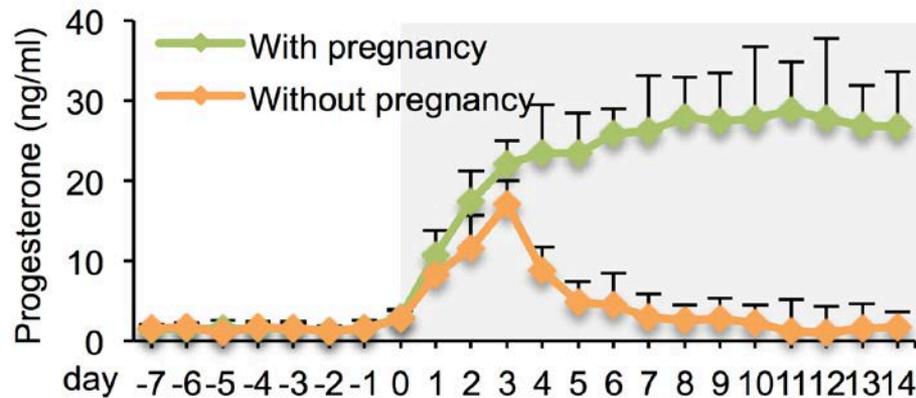
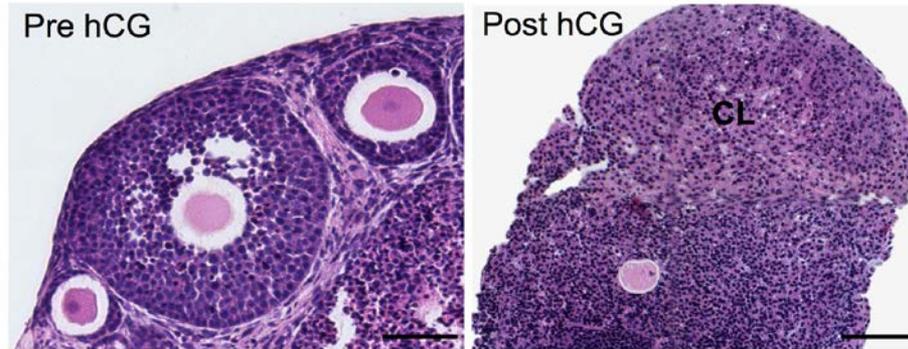
# Evatar™ Quintet-MFP™ Fallopian Tube Functioning



Xiao et al, *Nat Commun*, 2017.



# Quintet-MFP Supports Pregnancy-like Hormone Conditions

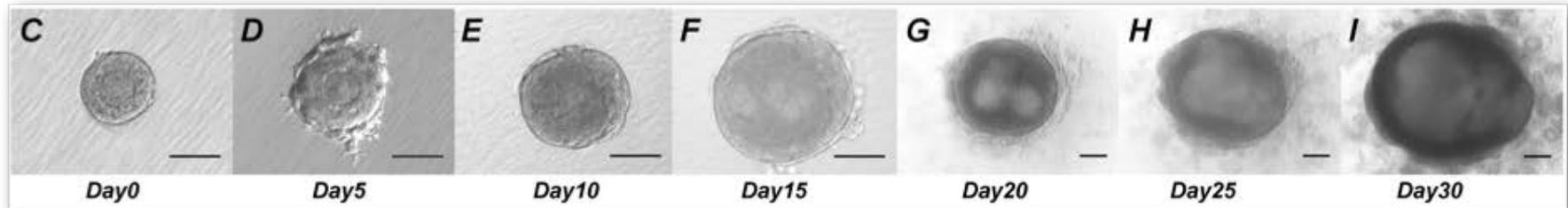
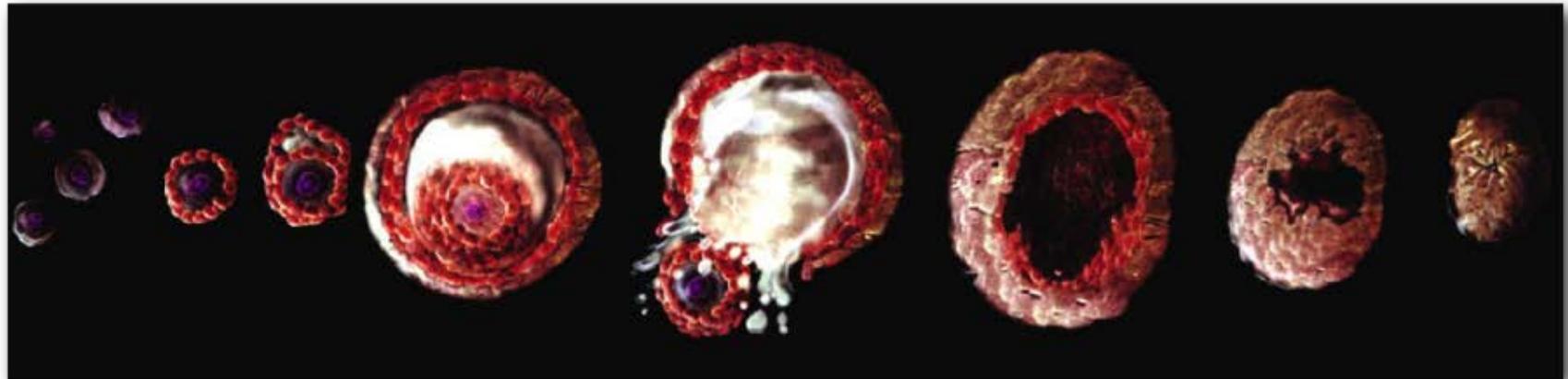


Reproductive tract physiology seems complicated...  
But it is an integrated system with functional hallmarks  
that can be modeled *in vitro*

Personalized Drug Testing  
Toxicology Testing  
Signaling Pathways  
Integrated Cell Biology



# Follicle maturation *in vitro* phenocopies *in vivo* development

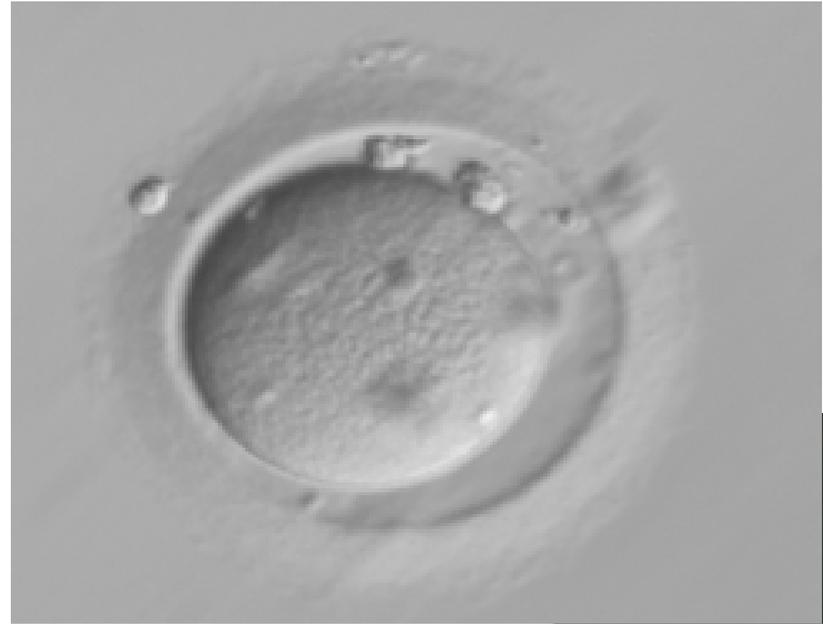


Grow - Secrete Hormones - Differentiate  
Egg Matures - Ovulatory Mechanics - Connections  
Live, Healthy Births in Mice  
Architecture, Environment and Hormones

# eIVFG Matured Human Oocytes

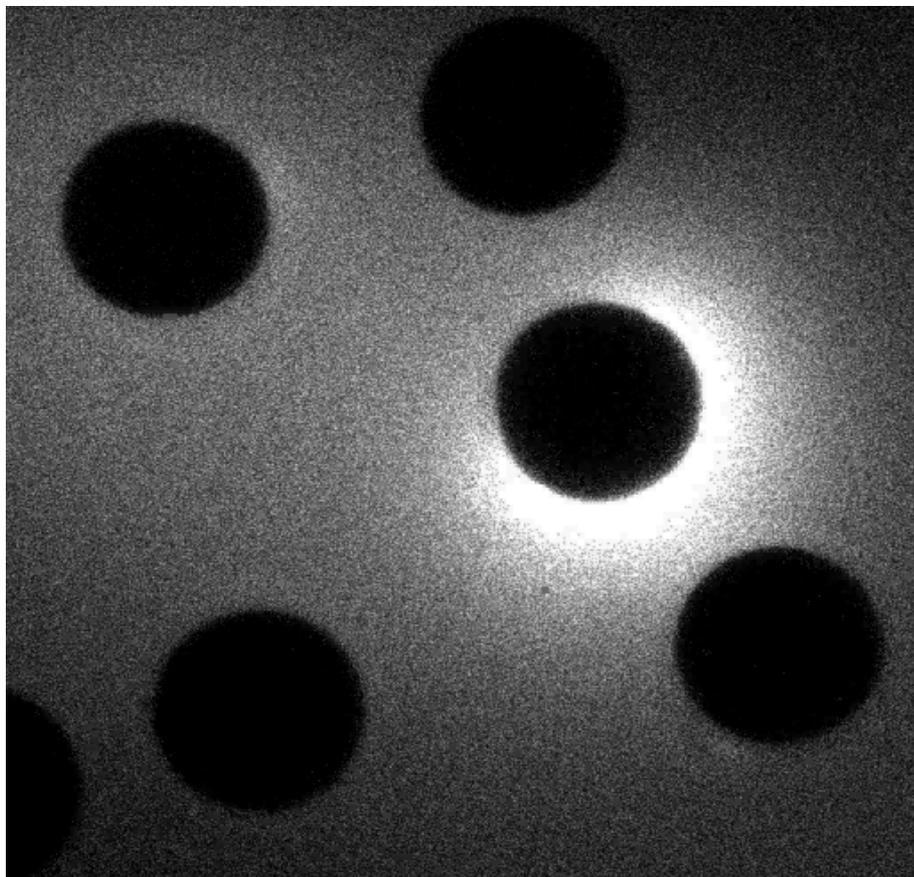


44 patients; 65 follicles; 4 MII



National Center for Translational Research in Infertility  
NICHD P50

# What Makes a Good Egg?



Kim, Bernhardt, Kong, Duncan, Que, Zhang, O'Halloran and Woodruff *Nature Chemistry*; *Nature Chemical Biology*; *Scientific Reports* (2009-present)



Francesca Duncan, Ph.D.  
Assistant Professor  
Northwestern University



# Challenges of basic reproductive research with human material

## Material that:

- 1) Is exceedingly rare and precious
- 2) Has the potential to give rise to the next generation
- 3) Has ethical limitations and legal restrictions for use

*The Dickey-Wicker Amendment prevents the federal funding of research that uses embryos “derived by fertilization, **parthenogenesis**, or any other means from one or more human gametes.”*

### RESEARCH FUNDING

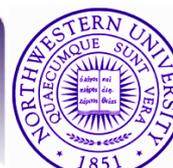
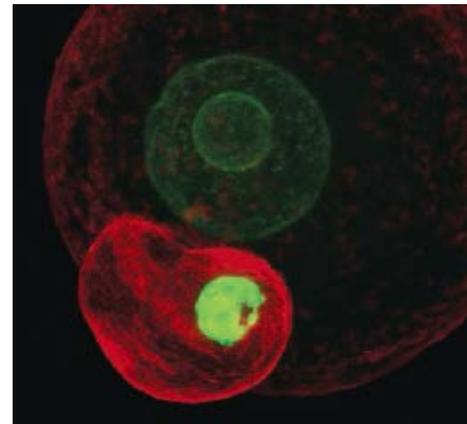
## Politics and Parthenotes

C. Tingen<sup>1\*</sup>, S. Rodriguez<sup>1,2\*</sup>, J. Campo-Engelstein<sup>1,2\*</sup>, T. K. Woodruff<sup>1†</sup>

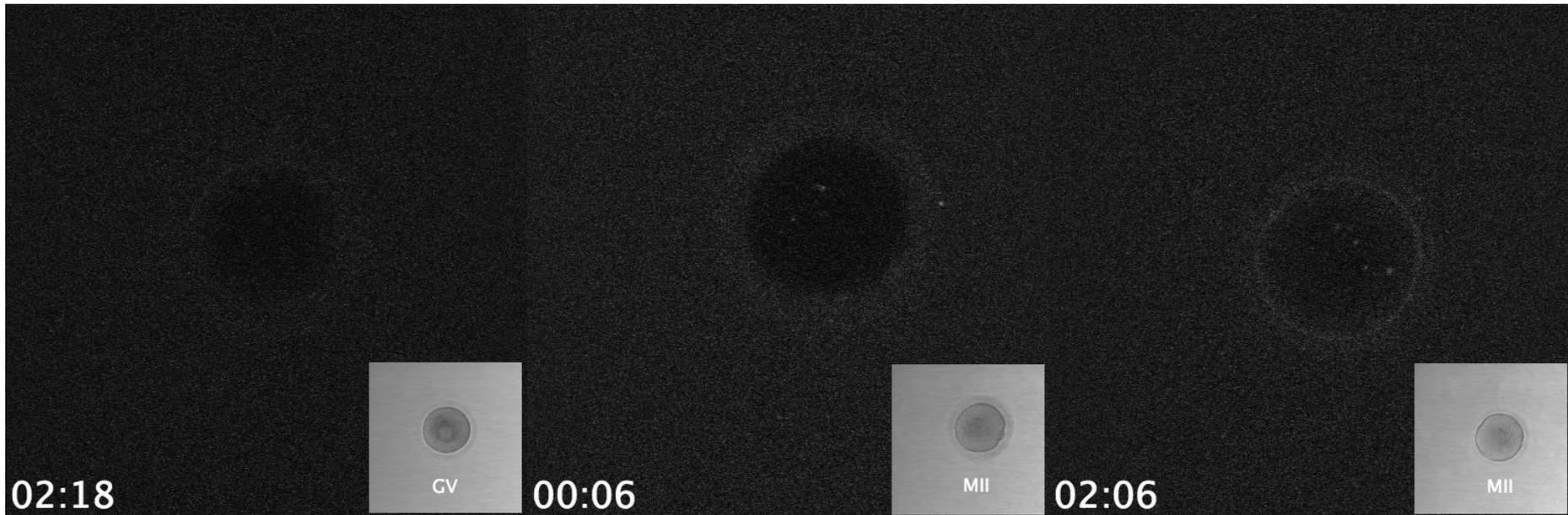
**POLICYFORUM**

Broad restrictions on funding for human embryo research can stymie work that was unnecessarily precluded by a flawed U.S. law.

SCIENCE VOL 330 22 OCTOBER 2010



# Zinc is only released from mature, health human eggs

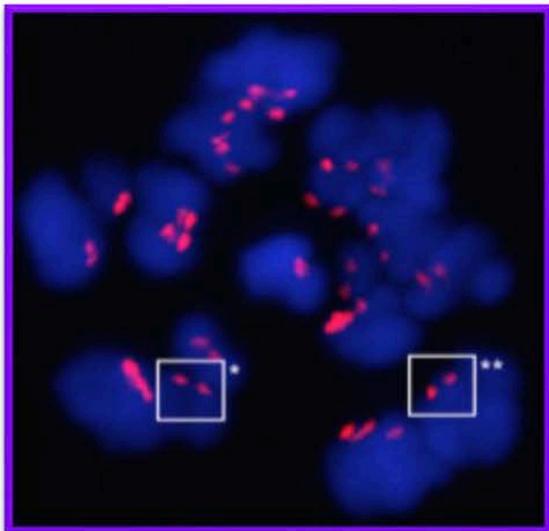


**The zinc spark is an inorganic signature of human egg activation**

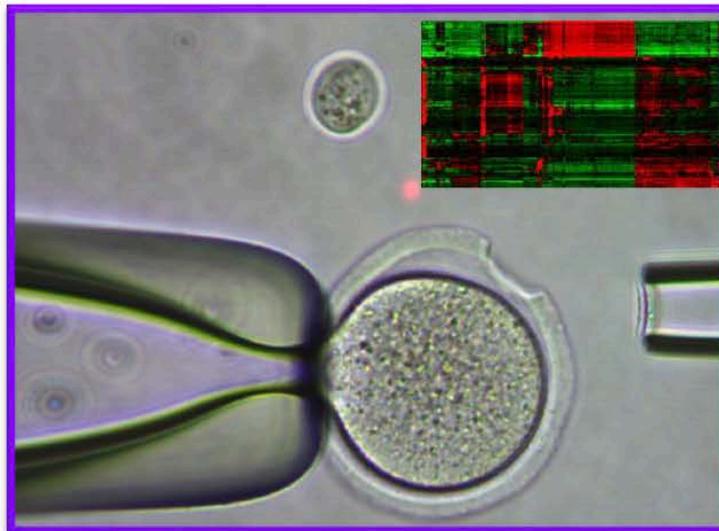
Francesca E. Duncan, Emily L. Que, Nan Zhang, Eve C. Feinberg,  
Thomas V. O'Halloran, Teresa K. Woodruff\* Scientific Reports, 2016

DISCOVER Magazine – Top 100 Discoveries of the Year

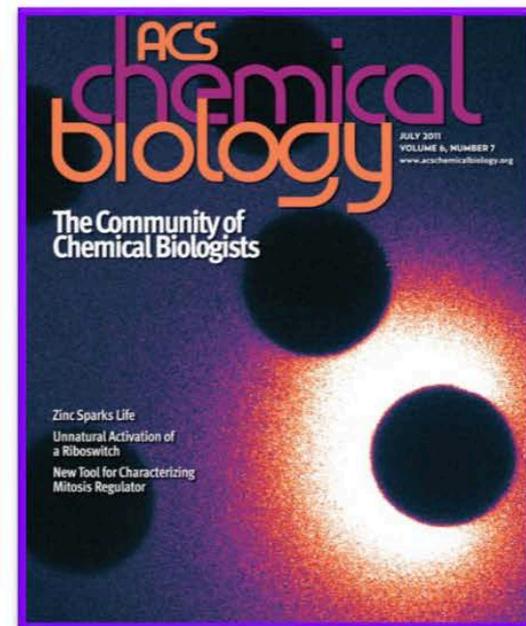
# What makes a good egg?



Chromosome  
number  
and Structure

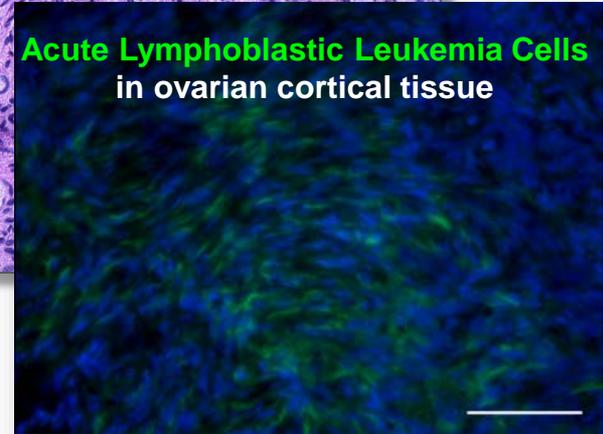
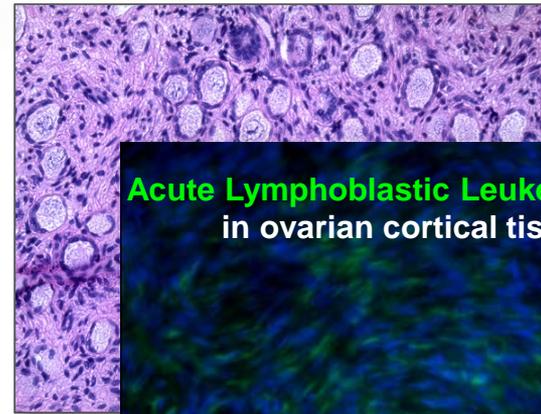
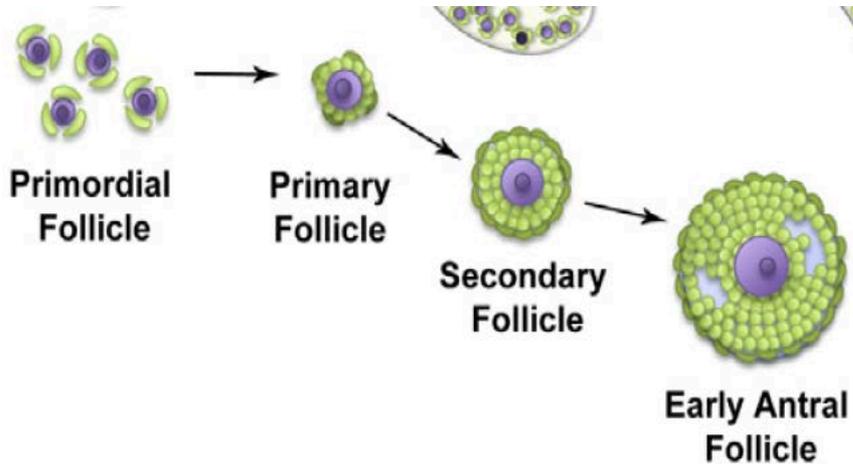
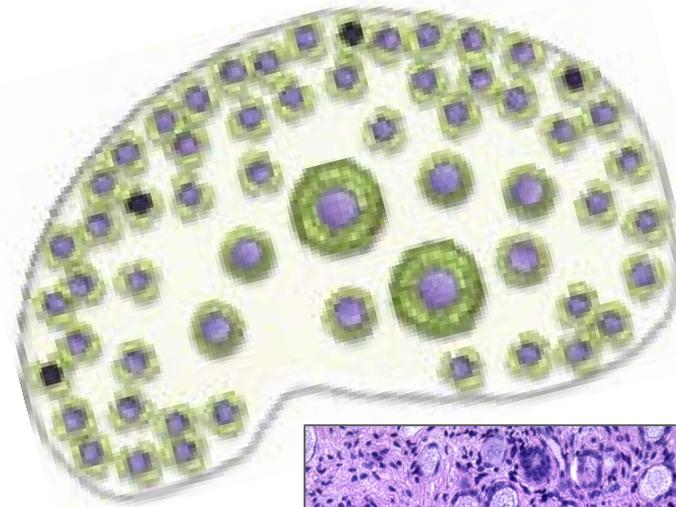


Oocyte-specific  
gene expression



Zn exocytosis  
at fertilization

# Fertility Needs in Pediatric Cancer Patients



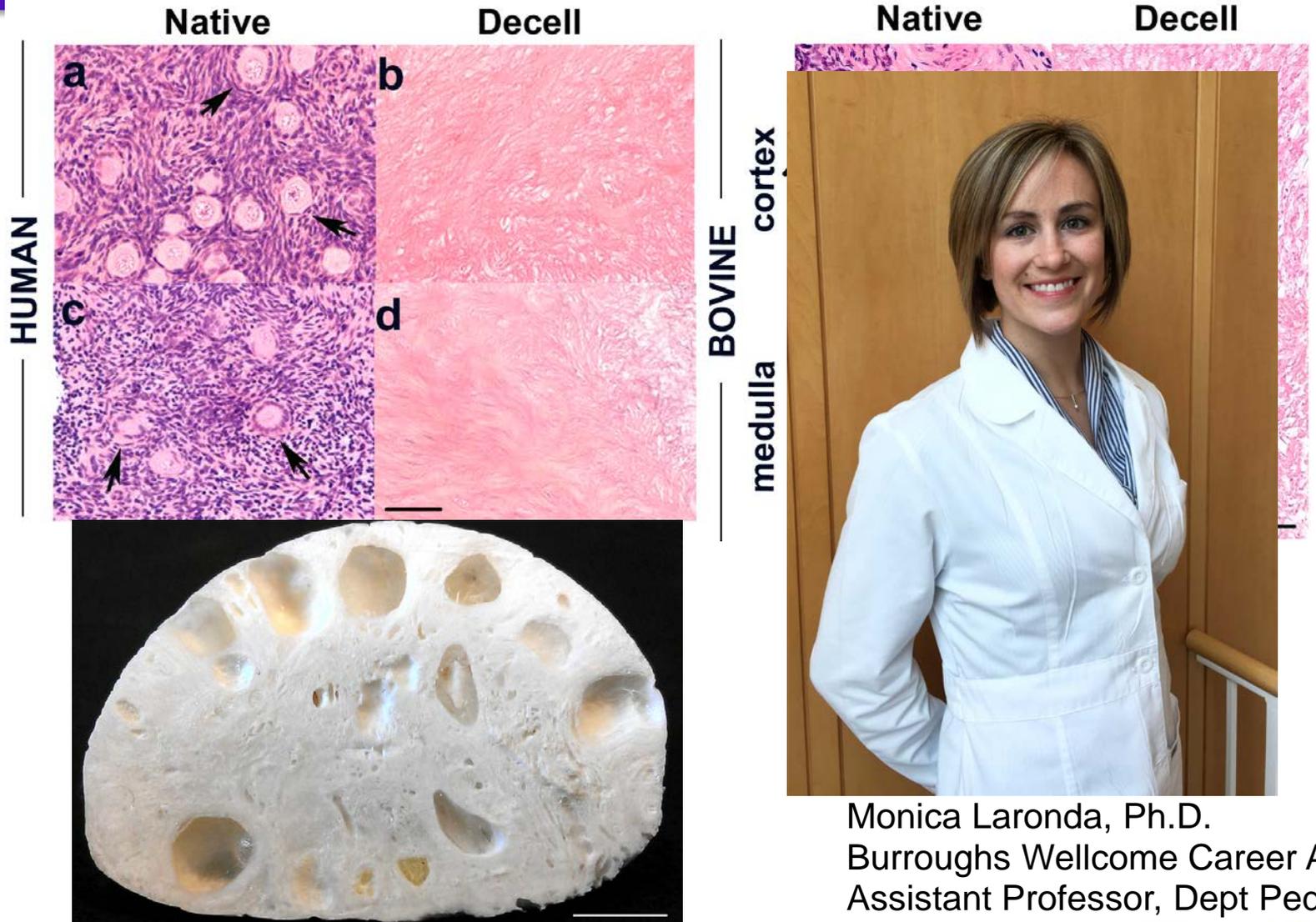
Ovarian cortical tissue from NPC participants; Scale bar = 50 um Laronda, et al. (2015) Biomaterials

Modified from: Cordeiro, Kim, Woodruff. *Cancer Treatment and the Ovary* (2015)

Patient Sample 4 y.o.; scale bar = 100 μm; National Physicians Cooperative



# Decellularized Ovary for Bio-active Scaffold



Monica Laronda, Ph.D.  
Burroughs Wellcome Career Awardee  
Assistant Professor, Dept Pediatrics, NU

# Bioinspired design of structural ECM as organ scaffolds

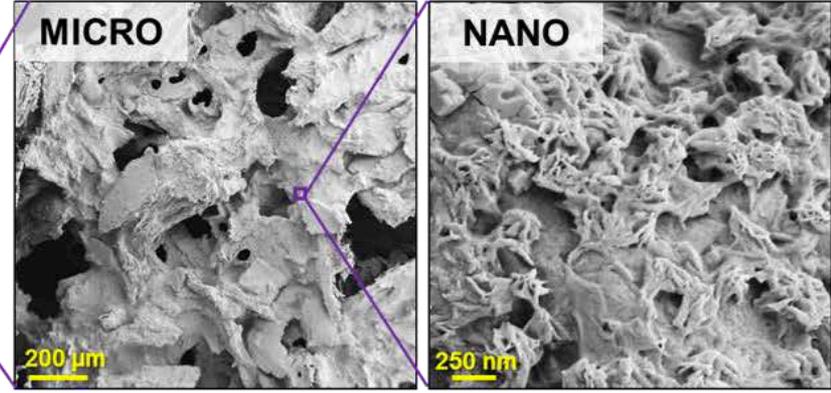
0.3 g dECM  
(~1 Ovary)



40 cm<sup>2</sup> TP  
<20 min. Fabrication

65 vol.% Ovary dECM  
35 vol.% PLGA

1 cm



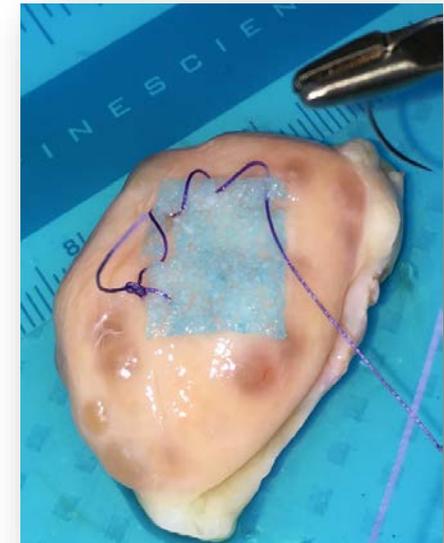
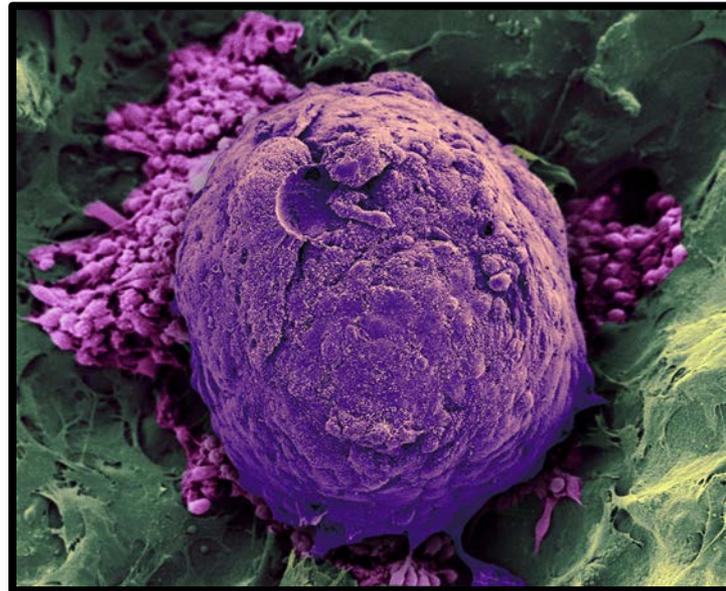
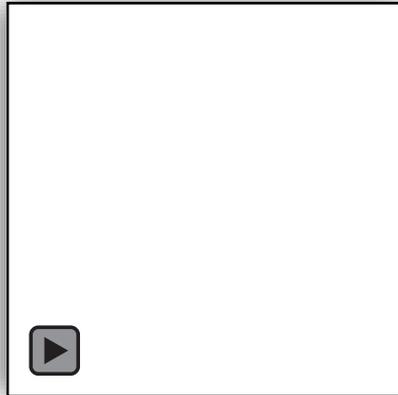
Retains substantial porosity and texture

Decell'd Bovine  
Ovary

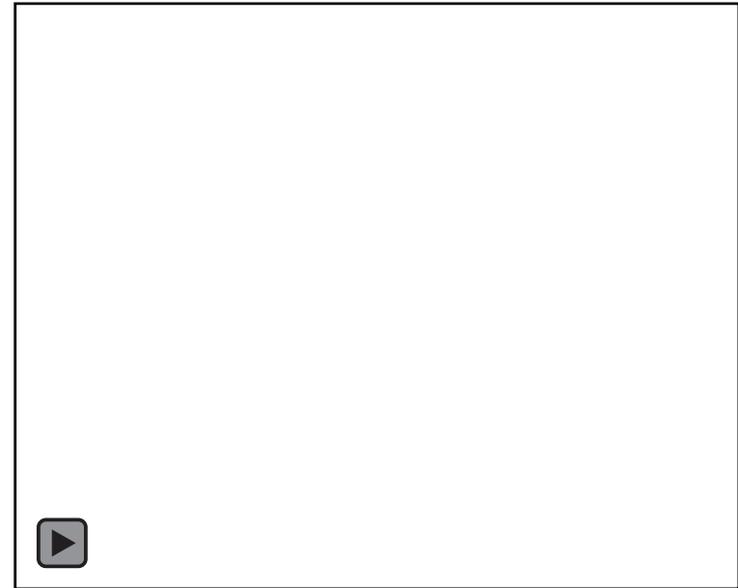
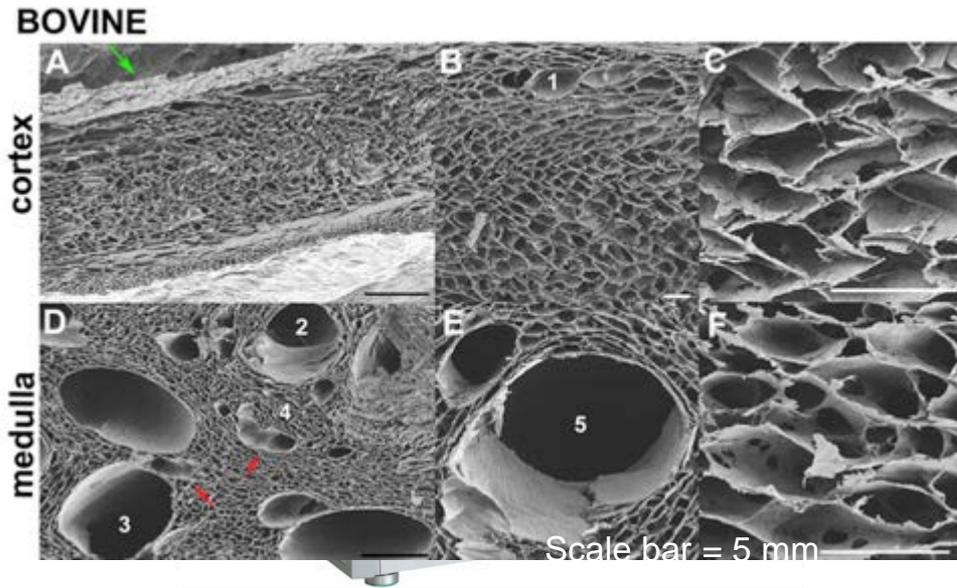
Powdered  
dECM

dECM  
"Ink"

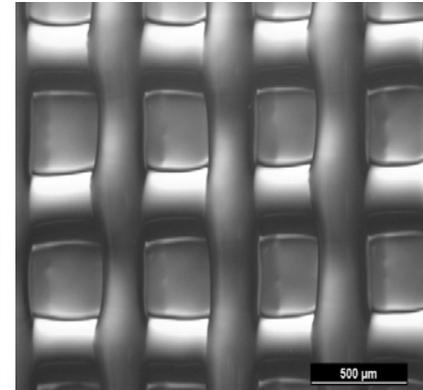
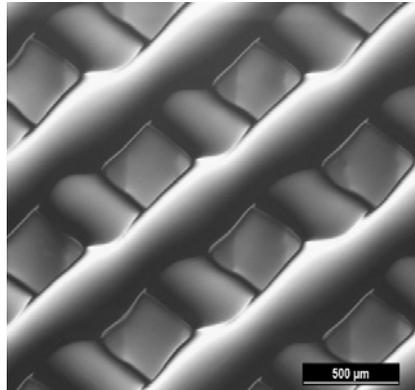
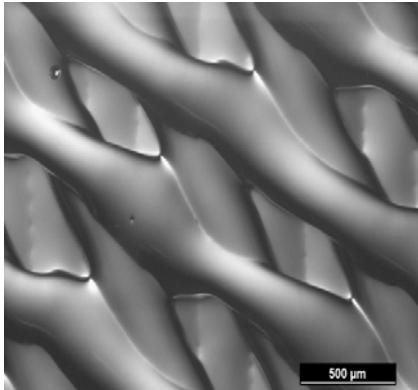
Ovarian dECM  
"Tissue Paper"



# Bioinspired design of structural ECM as organ scaffolds

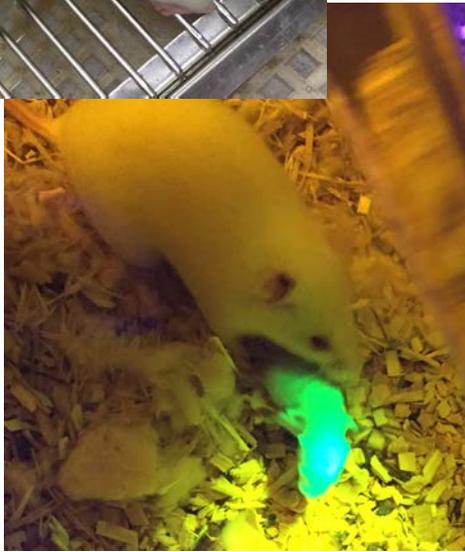


**30° advancing angle    60° advancing angle    90° advancing angle**



# Live Birth from Ovarian Bioprothesetic Transplant

(first soft organ transplant)



Transplant recipient (EGFP-)  
with EGFP+ pup

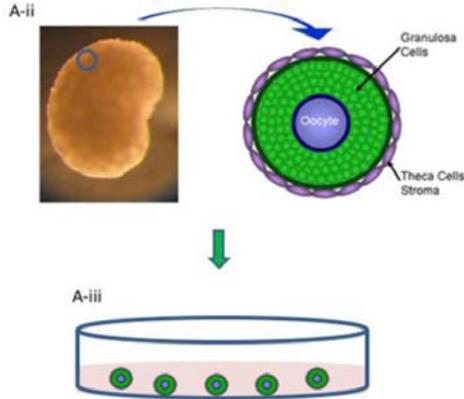


EGFP+ pup with  
CD1 pup from different litter



# Engineering the Reproductive Axis

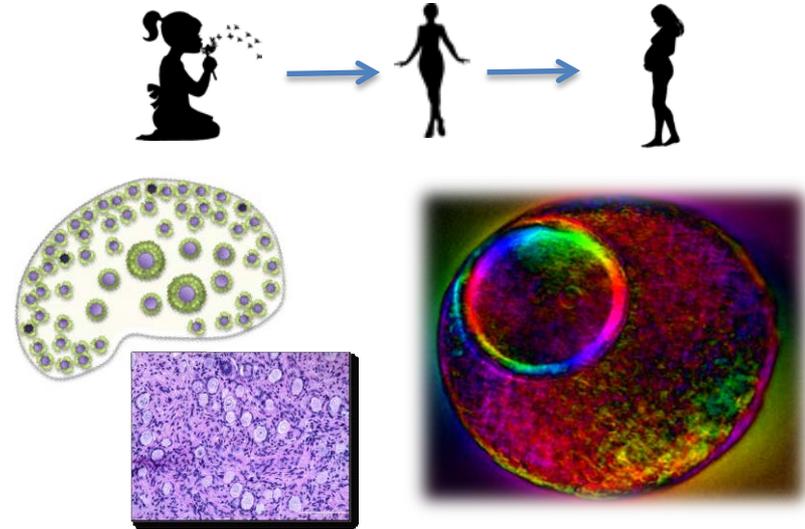
## Follicle Maturation in a Dish



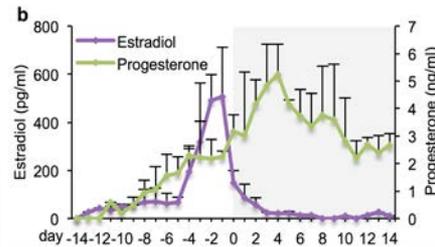
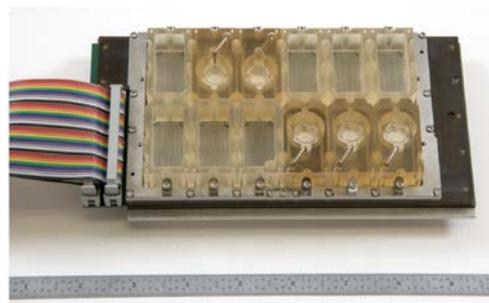
## NUBorn & NUAge



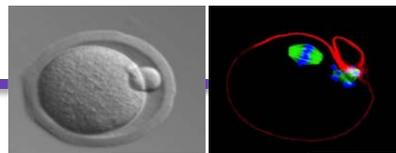
## Oncofertility Solutions



## Engineered Reproductive Tract

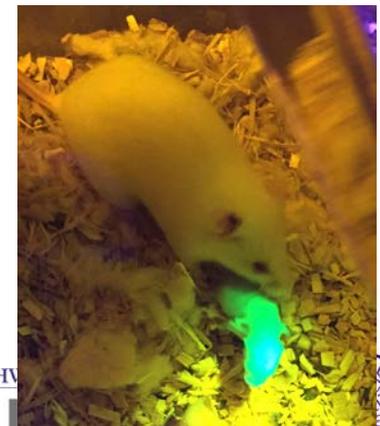


## MFP-Ovulation



## Artificial Ovary

### Decellularized Ovary



# Oncofertility 2017



- ✓ Global Oncofertility Community
- ✓ Human MII Eggs from eIVFG
- ✓ Human Zinc Spark
- ✓ Ovarian Cycle in a Dish
- ✓ Ovarian (Transplant) Bioprosthesis
  - ✓ Live Birth in Mice

We seek **solutions**. We don't seek  
- dare I say this - just scientific  
papers any more.

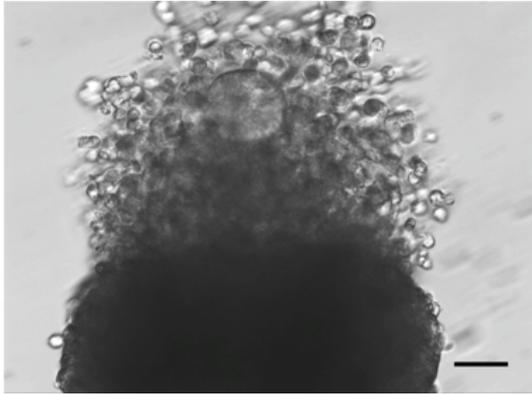
Steven Chu, March, 2009

# Oncofertility 2027



- ✓ Better Cancer Control and Tx
- ✓ Higher Selectivity of Patients
- ✓ Neo-adjuvant Fertoprotectives
- ✓ In Vitro Follicle Maturation
- ✓ Designer Ovarian Bioprosthesis
- ✓ Eliminate the Field

I have been taught that the way of progress is neither swift nor easy.  
Marie Curie, 2021



# Bench to Bedside

NATIONAL  
PHYSICIANS  
COOPERATIVE

 the  
Oncofertility®  
Consortium  
[www.oncofertility.northwestern.edu](http://www.oncofertility.northwestern.edu)

GLOBAL  
ONCOFERTILITY  
NETWORK

# Thank you!



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Oncofertility Consortium  
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Microfluidic Menstrual Cycle  
NCATS/ORWH/NIEHS: UH3TR001207

Zinc Spark  
NIGMS: R01GM115848; Keck Foundation;  
Argonne National Laboratories

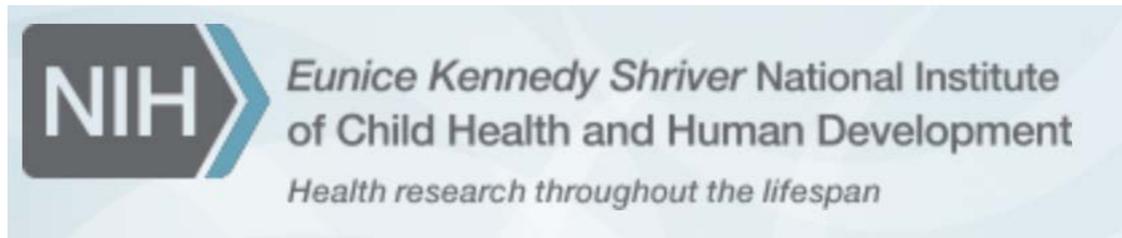
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Woodruff Lab Past and Present



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*Thank you!*

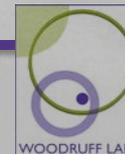


# NIH Office of Research on Women's Health (ORWH)





Visit us at:  
<http://woodrufflab.org/>  
<http://oncofertility.northwestern.edu/>

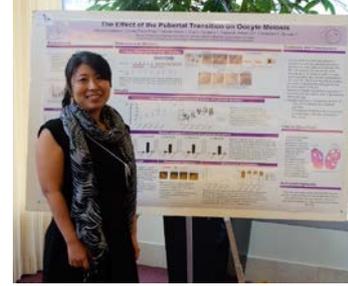
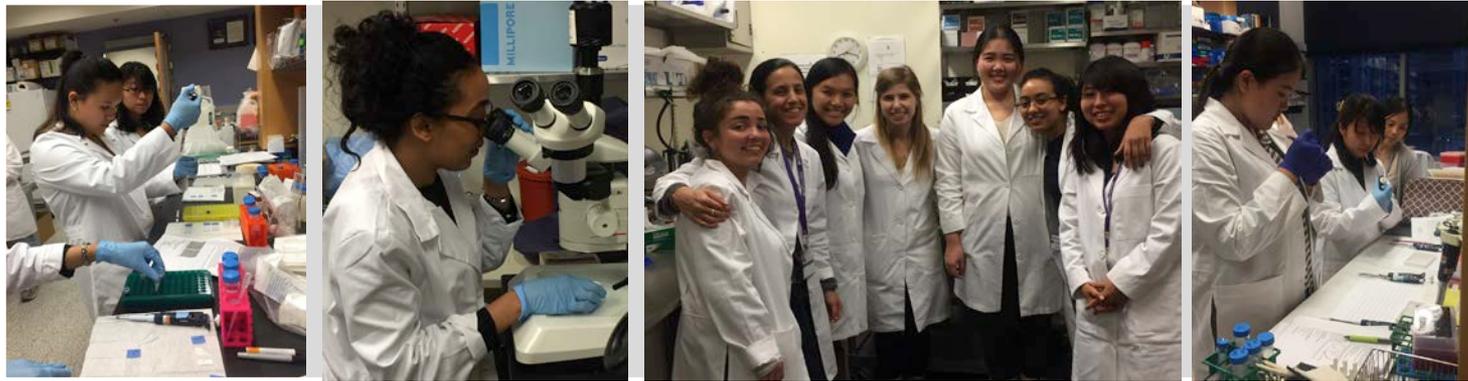


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## INQUIRIES:

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