

Engineering Reproduction

Teresa K. Woodruff, Ph.D.

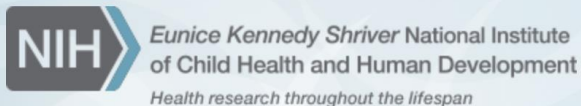
Thomas J. Watkins Memorial Professor and Vice Chair for Research

Department of Obstetrics and Gynecology

Chief, Division of Reproductive Science in Medicine

Northwestern University Feinberg School of Medicine

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



Preservation of Fertility After Cancer

- Life preserving treatments

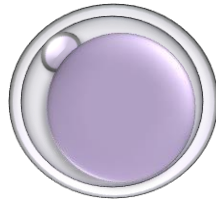
- Chemotherapy
- Radiation
- Surgery

- Can threaten fertility

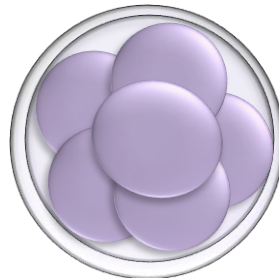


Jeruss & Woodruff **N Engl J Med** 2009;
Woodruff **Nature Medicine** 2009;
Woodruff **Nature Rev Clin Oncol**, 2010;
Woodruff, **Nature Rev Endocrinol**, 2013;
DeVos, Smitz, & Woodruff, **Lancet**, 2014;
Gradishar, Smith, & Woodruff, **JAMA Oncol**, 2016

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 Transplant: >86 Human Births



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

Efficiency - Cancer Recurrence

Fertility and Endocrine Needs of Pediatric Cancer Patients

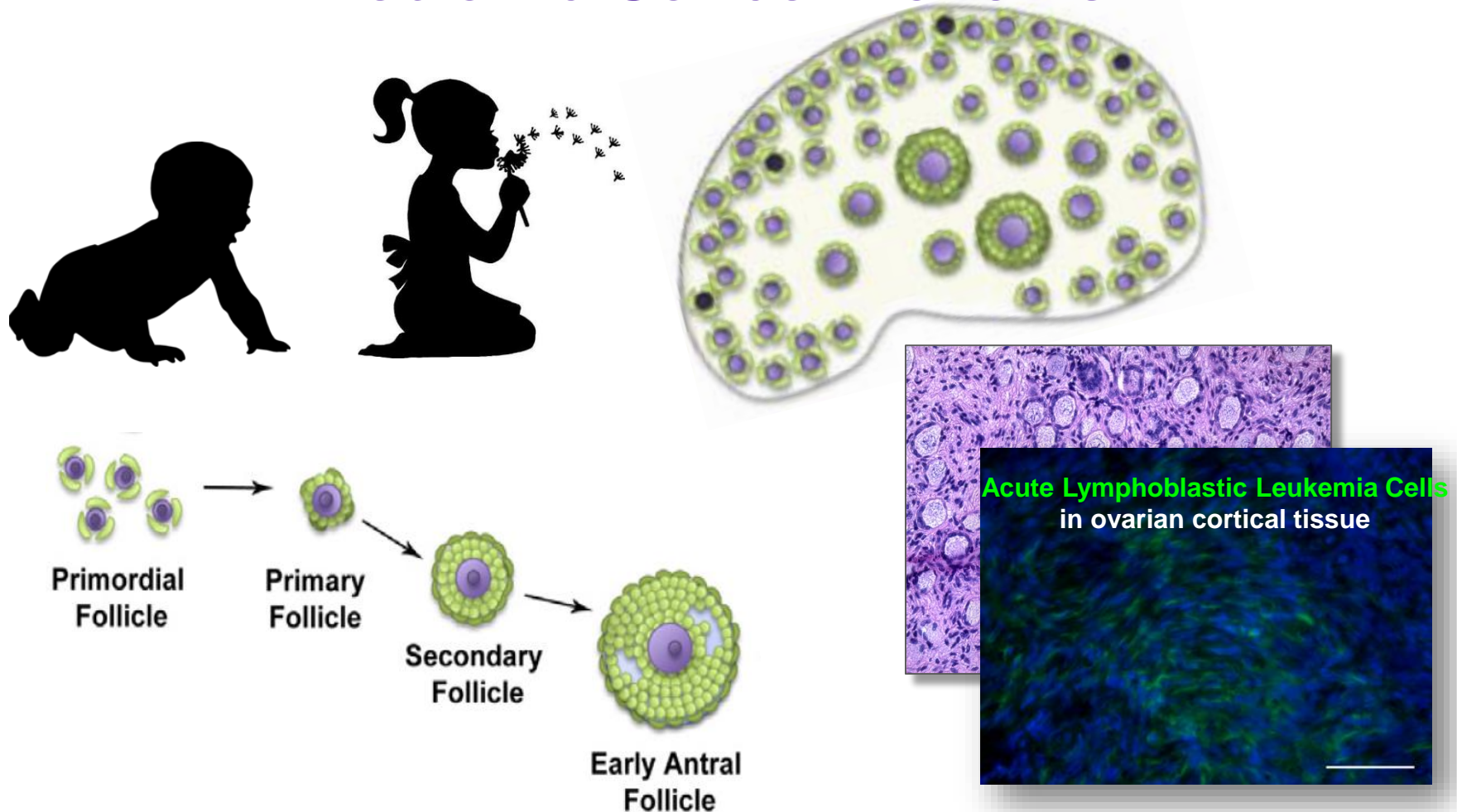
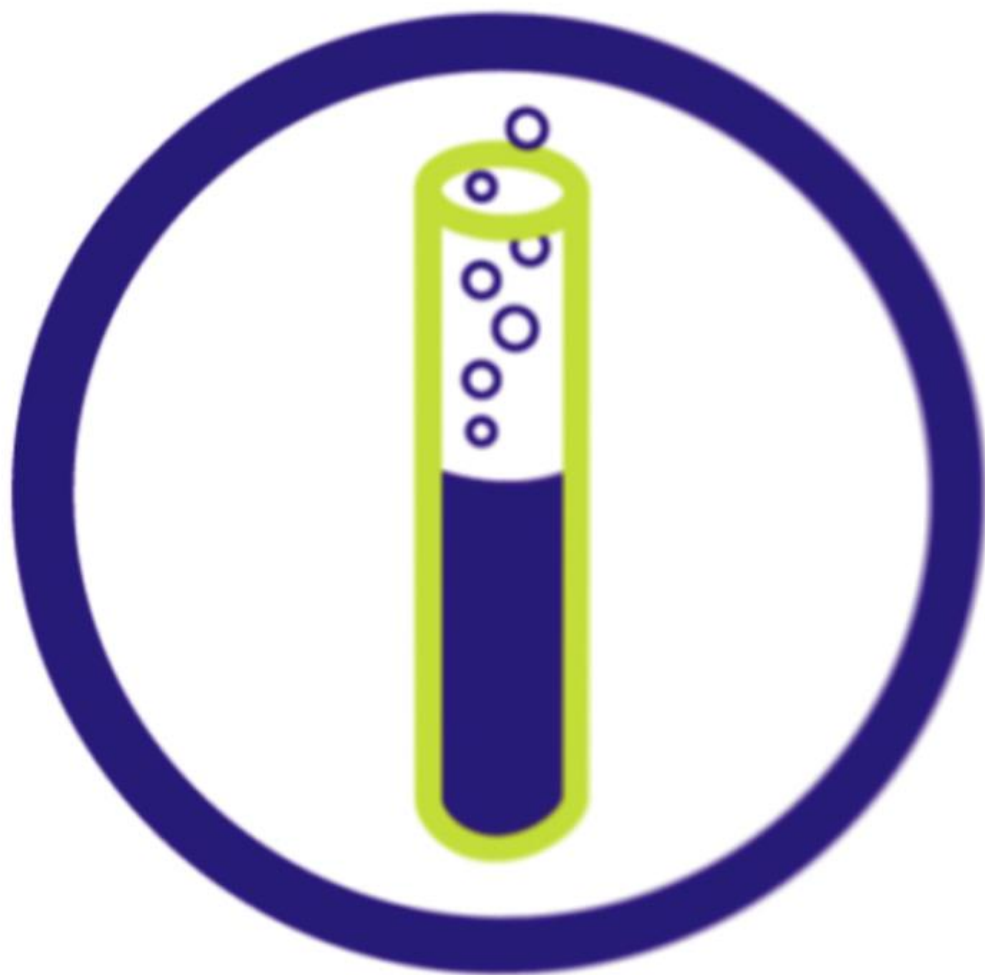


Figure in: Cordeiro, Kim, Woodruff. *Cancer Treatment and the Ovary* (2015)
Patient Sample 4 y.o.; scale bar = 100 μ m; National Physicians Cooperative
Laronda, et al. (2015) Biomaterials



RESEARCH

NATIONAL
PHYSICIANS
COOPERATIVE



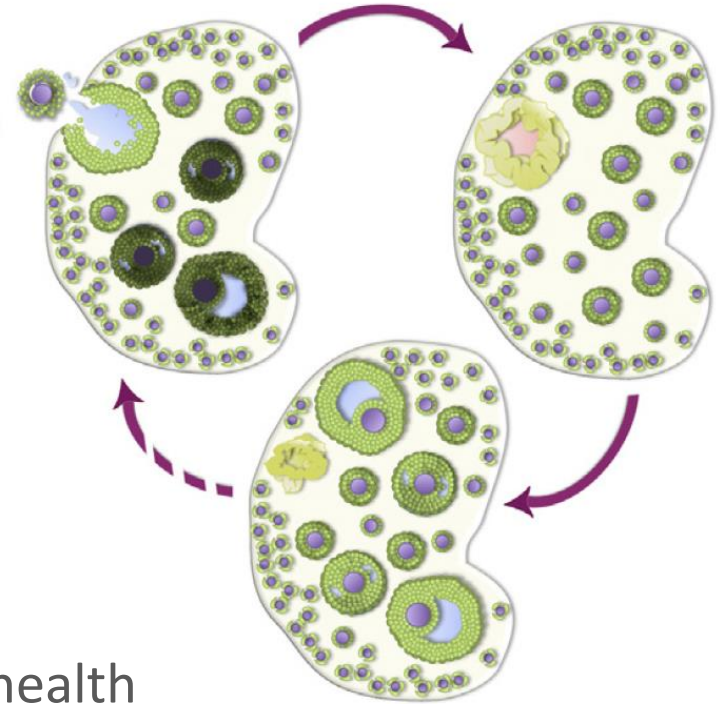
the
Oncofertility[®]
Consortium

www.oncofertility.northwestern.edu

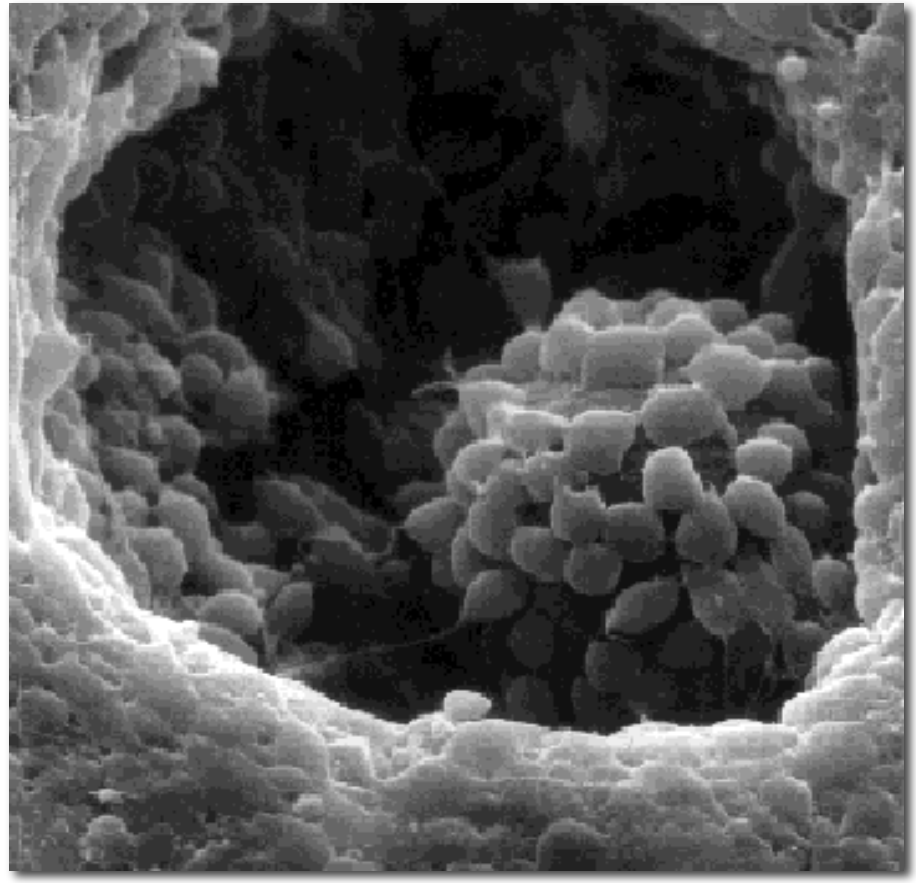
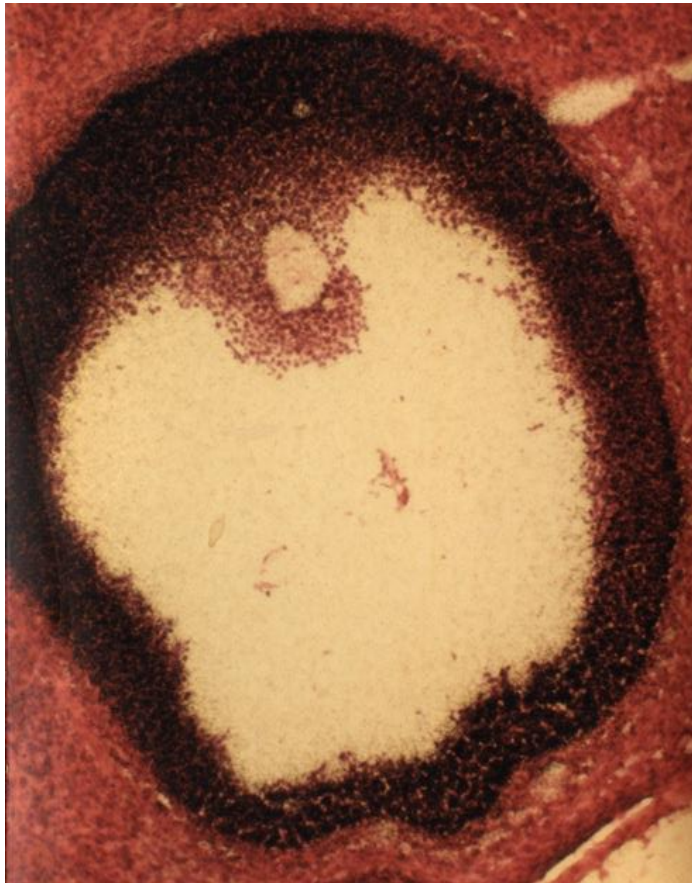
GLOBAL
ONCOFERTILITY
NETWORK

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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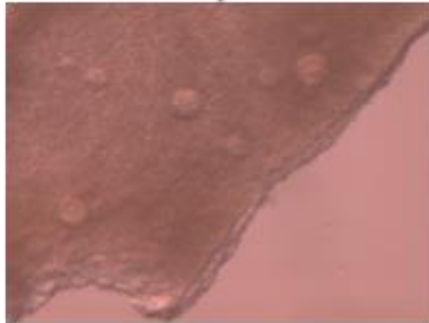
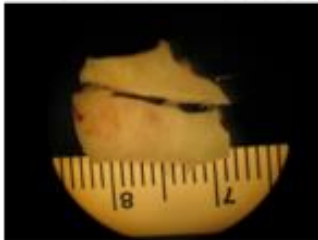


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Consortium
www.oncofertility.northwestern.edu

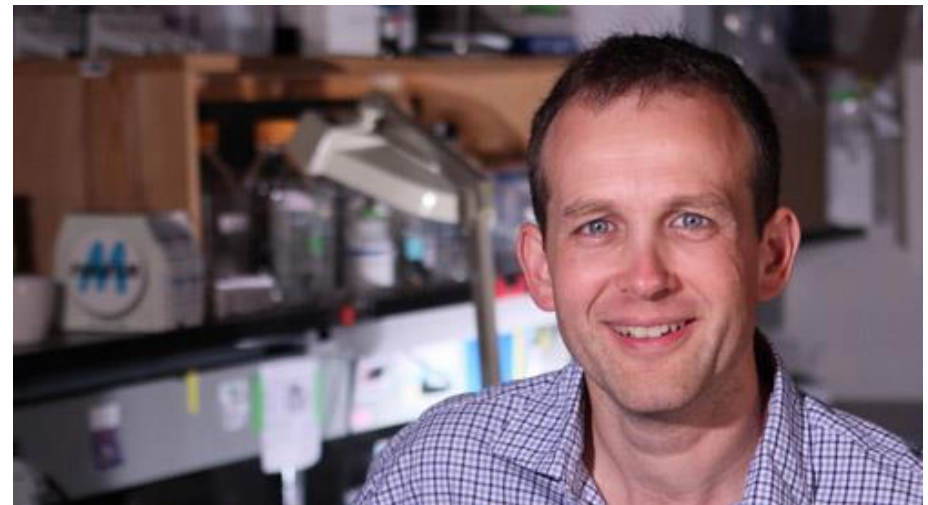
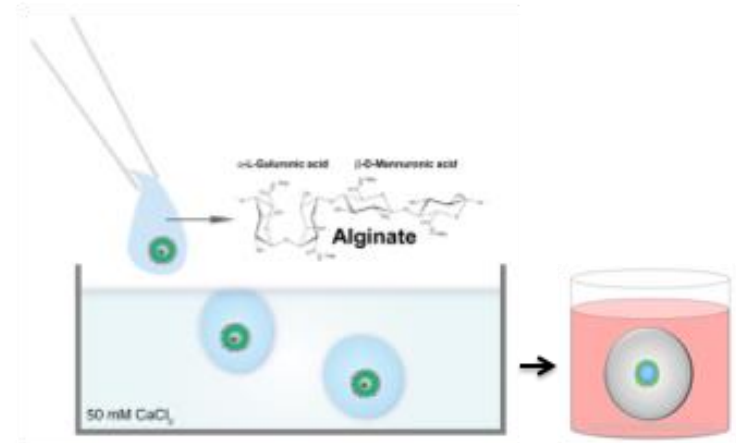
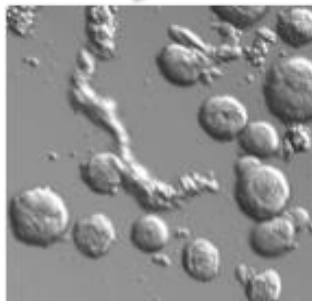
GLOBAL
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NETWORK

Encapsulated In Vitro Follicle Growth (eIVFG)

Ovarian tissue



Isolated follicles



Lonnie Shea, Ph.D.

Woodruff and Shea, 2000-present

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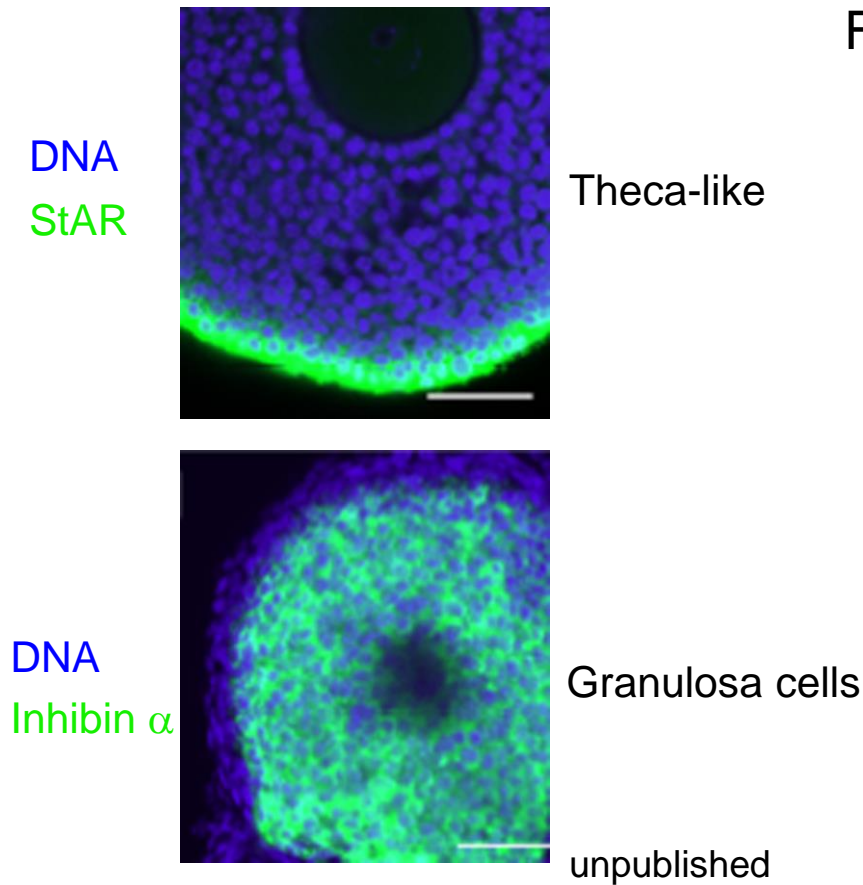


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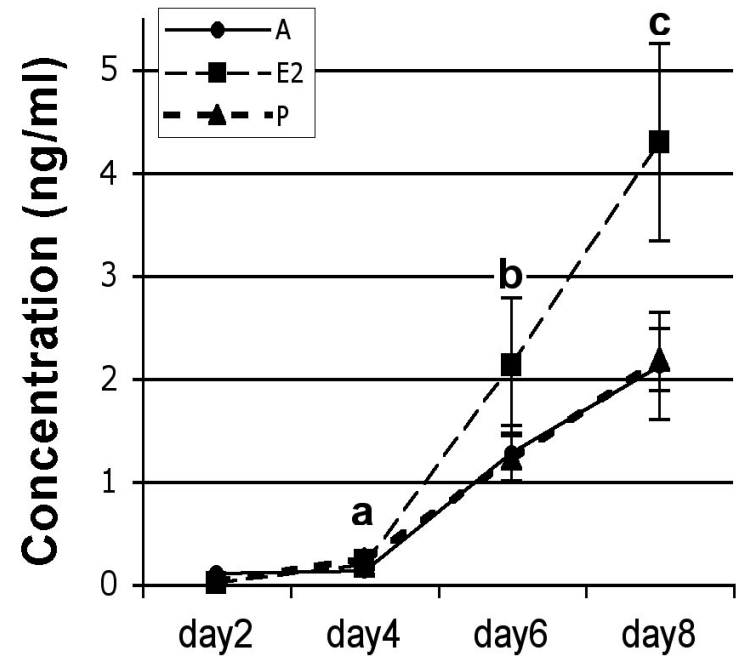
GLOBAL
ONCOFERTILITY
NETWORK

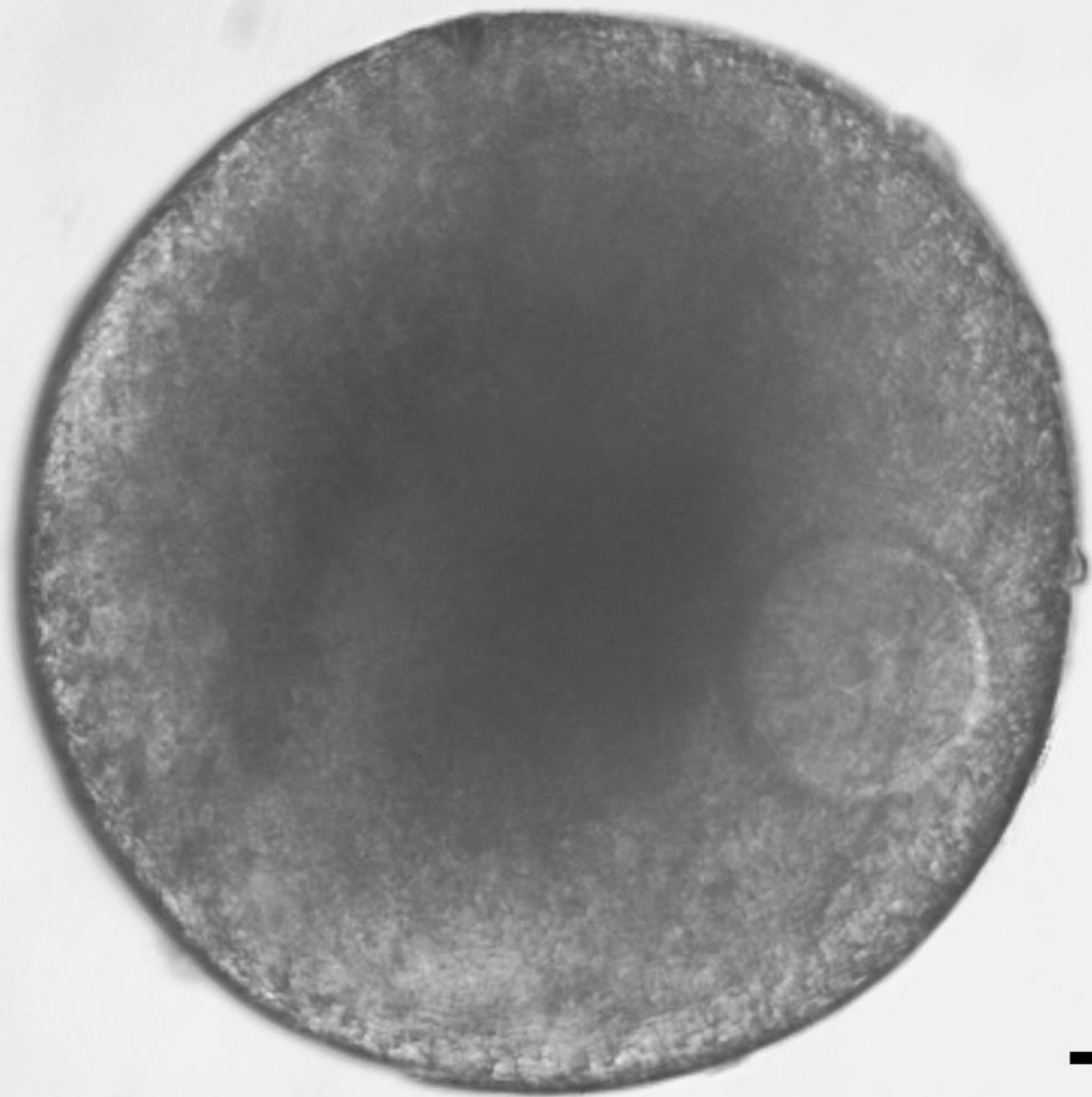
Encapsulated In Vitro Follicle Growth (eIVFG)

Two somatic cell compartments



Follicles produce steroid hormones

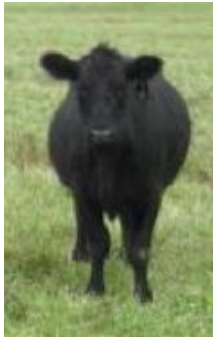




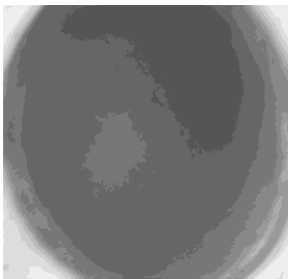
Encapsulated *in vitro* follicle growth systems in basic reproductive research



Cow



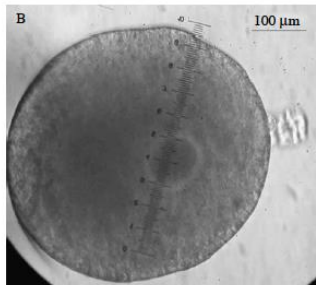
Follicle growth



Dog



Eggs & embryos



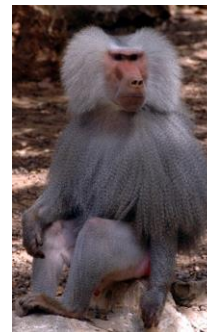
Rhesus macaque



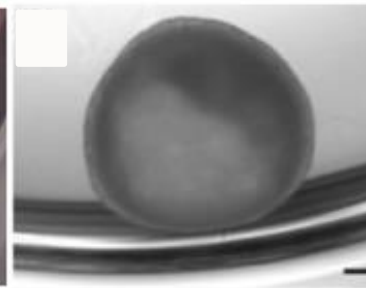
Eggs & embryos



Baboon



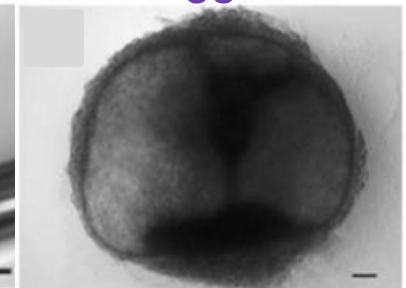
Eggs



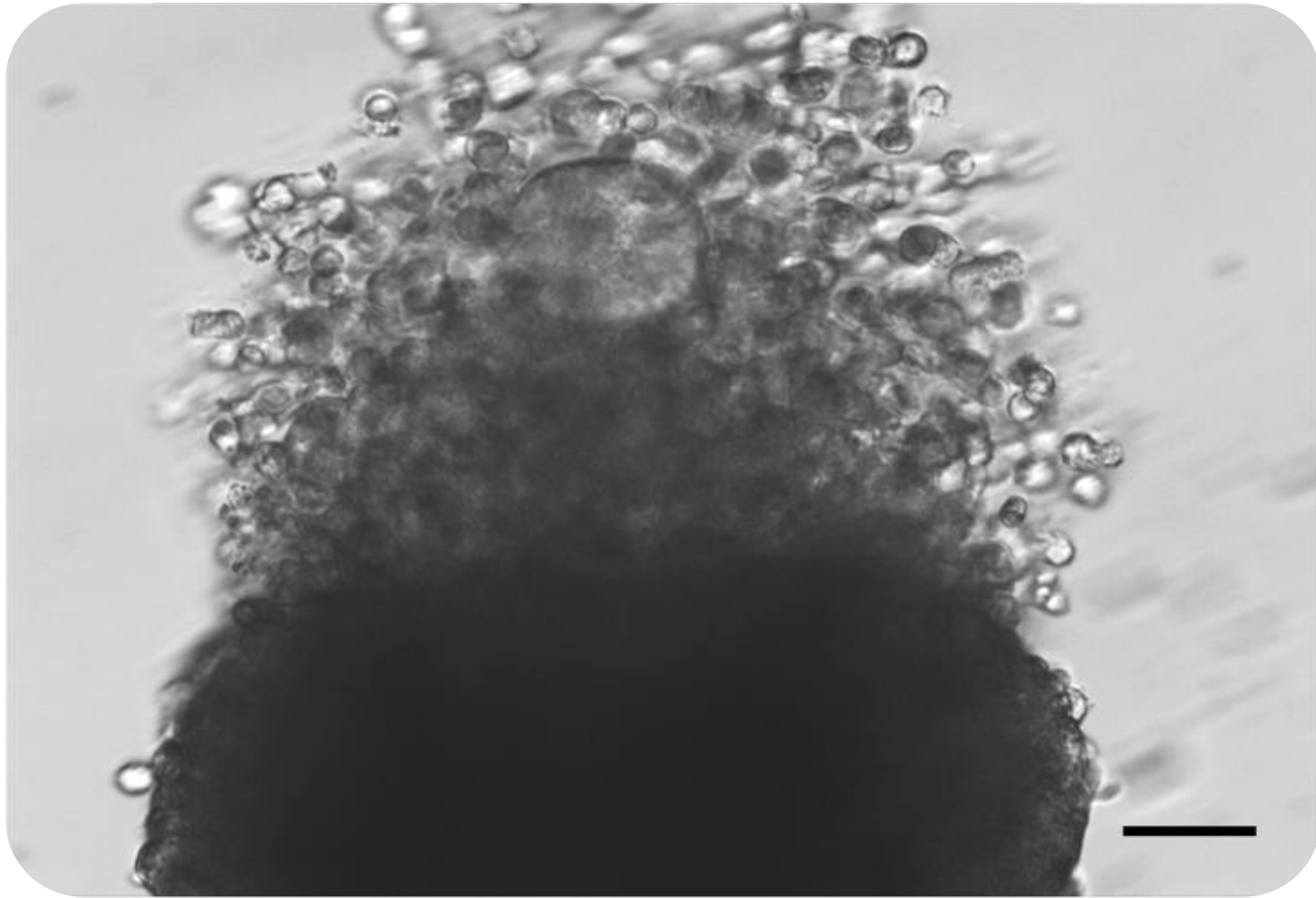
Human



Stage IV oocytes
& eggs

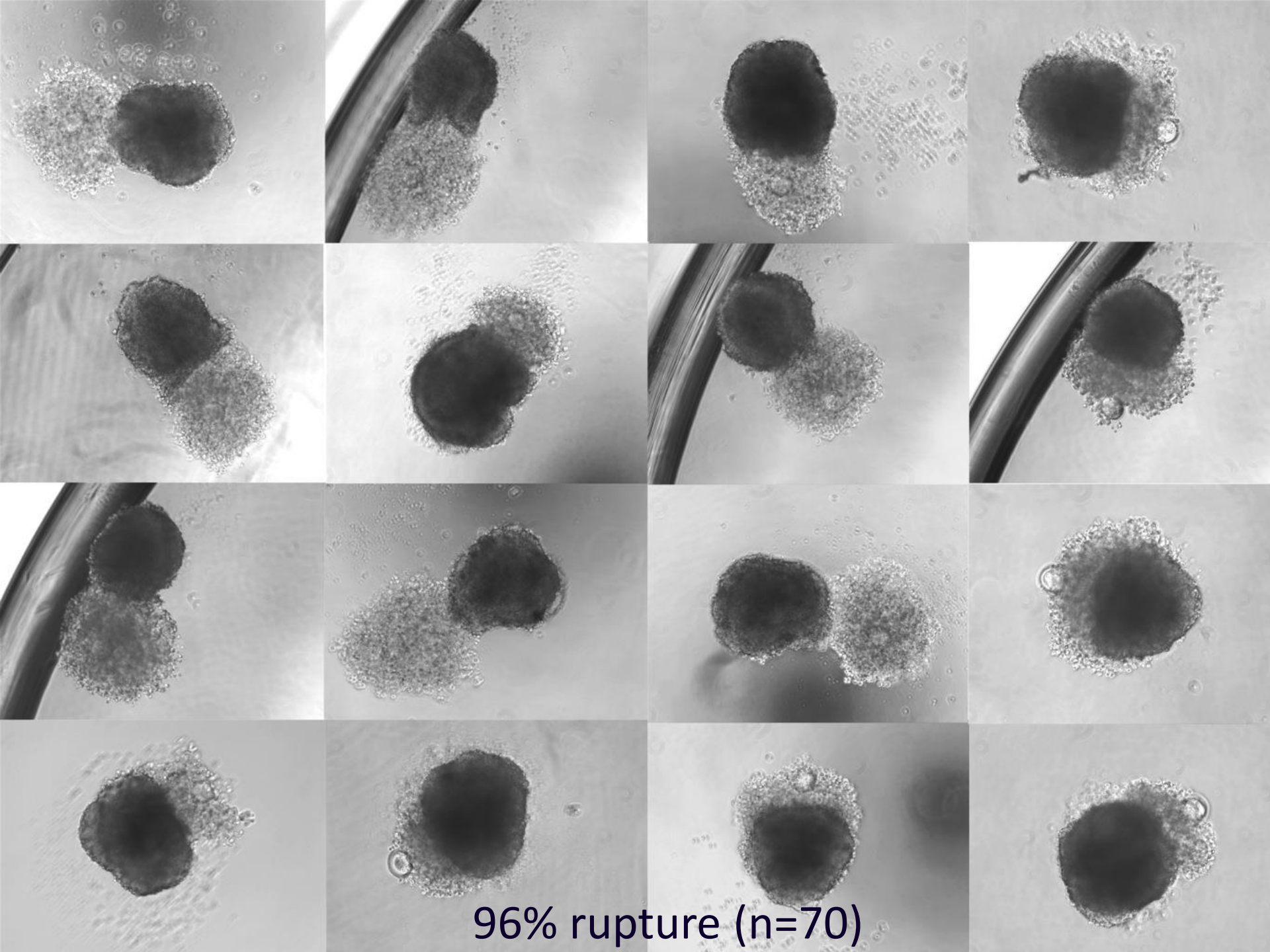


In Vitro Ovulation



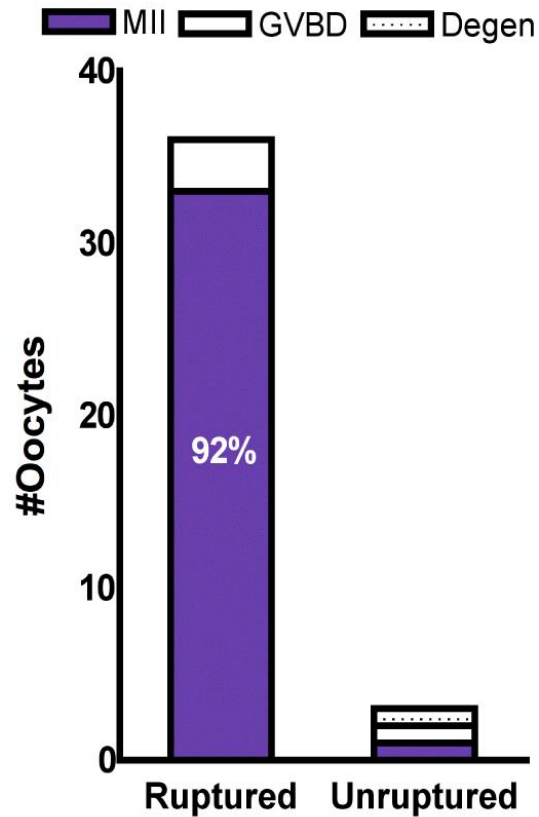
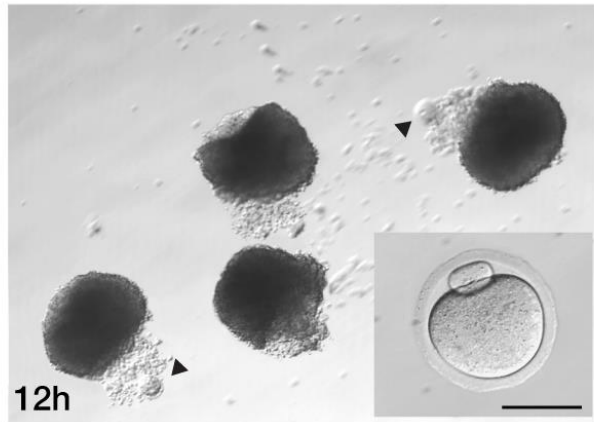
Skory, Xu, Shea and Woodruff, *Human Reprod.* 2015





96% rupture (n=70)

In Vitro Ovulation and Luteinization

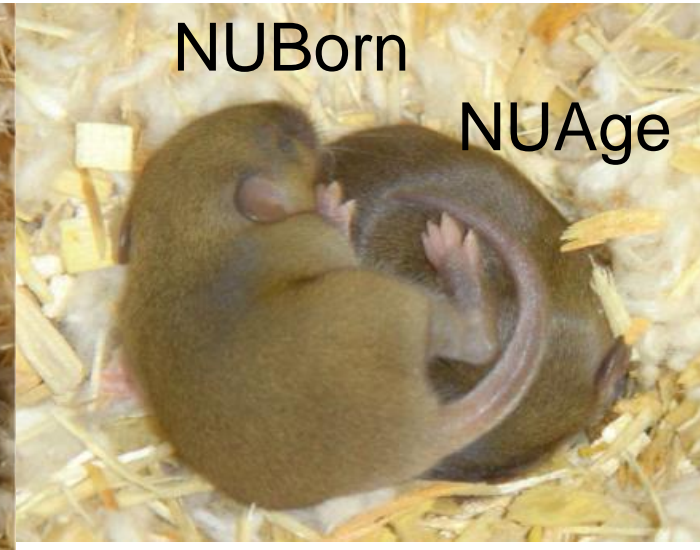


eIVFG Produces MII Eggs and Supports Live Birth

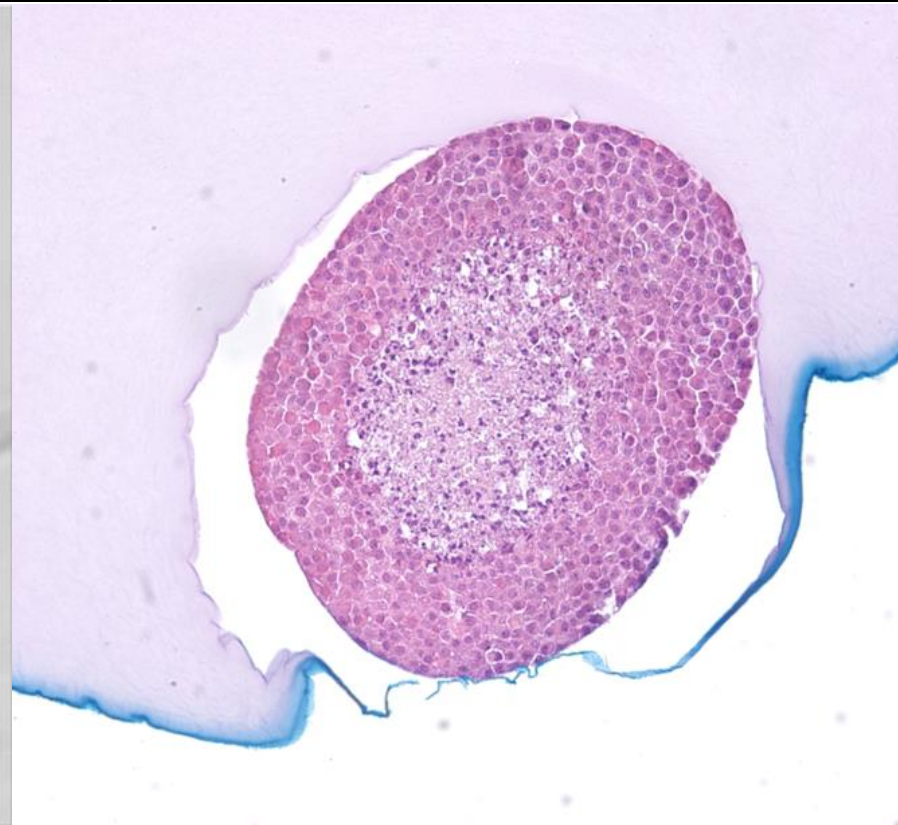
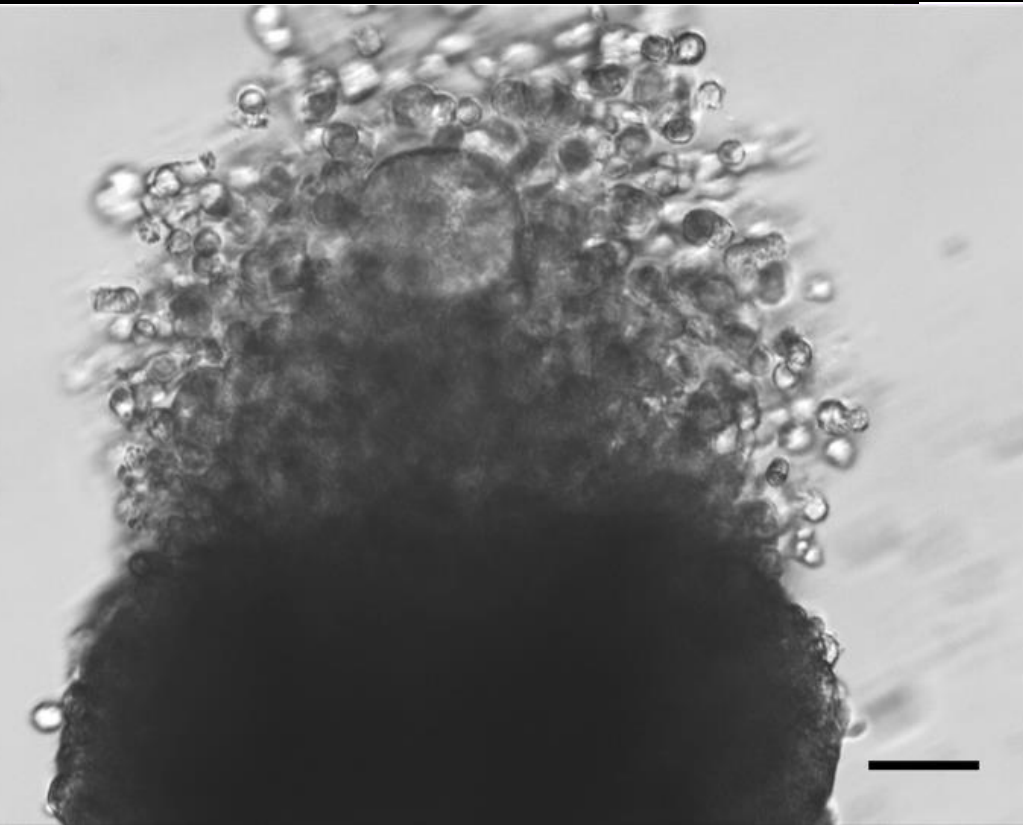
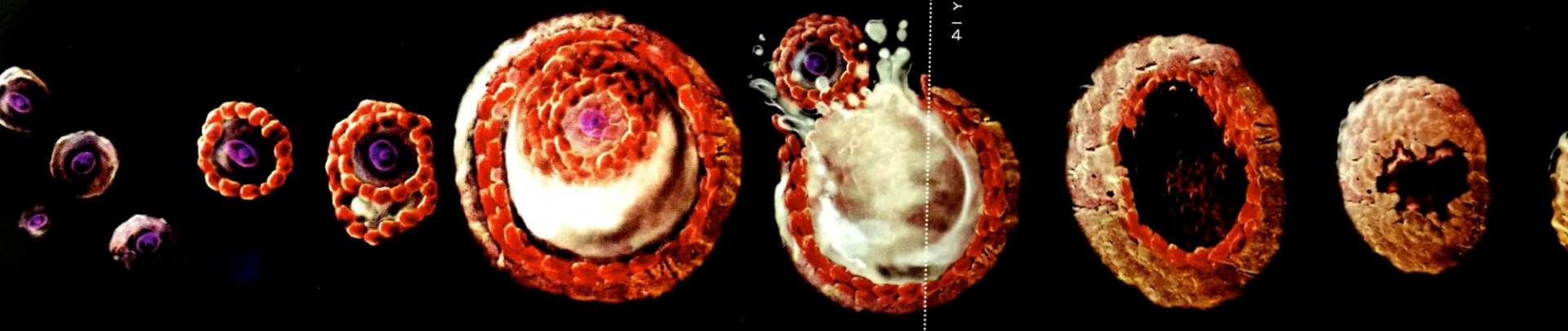
nature medicine

REPRODUCTIVE BIOLOGY

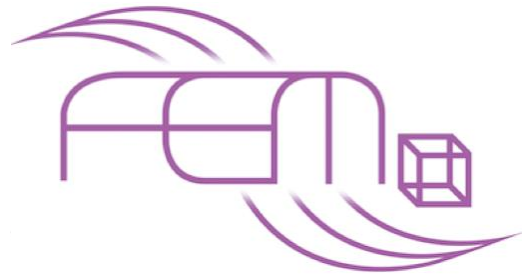
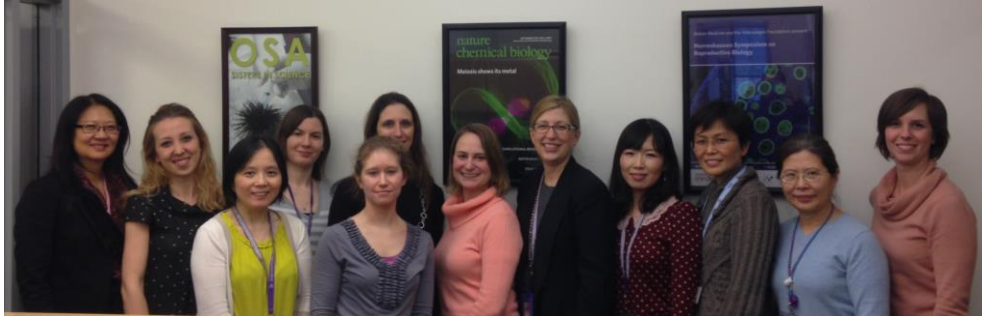
Supported by:
Barroughs Wellcome Fund and March of Dimes



Nature Medicine Breakthrough of the Decade (1998-2008)



Ex-Vivo Female Reproductive Tract Integration in a 3D Microphysiologic System - UH2ES022920/UH3TR001207



FemKUBE: Engineering
Reproductive Solutions

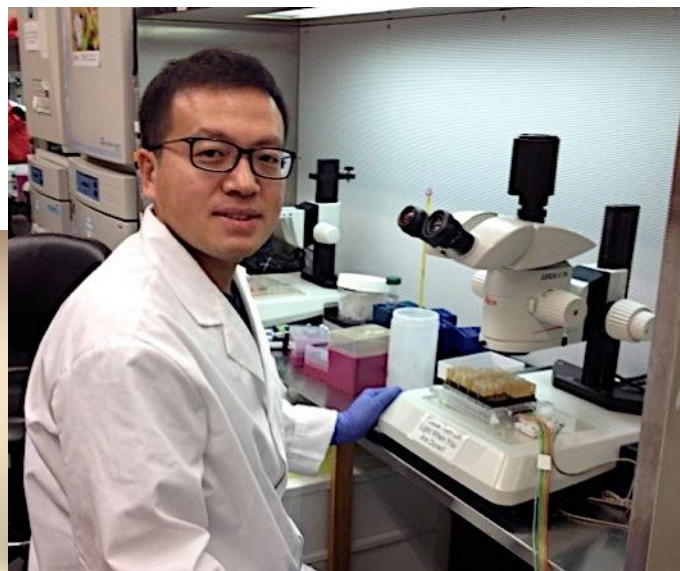


Eddie et al. *Experimental Biology and Medicine*, 2014
Laronda et al. *Stem Cell Research and Therapy*, 2014
Xiao, et al. *Nature Communications*, 2017





Hunter Rogers, Graduate Student



Shuo Xiao, Ph.D. Postdoc 2013-2016
Assistant Prof USC

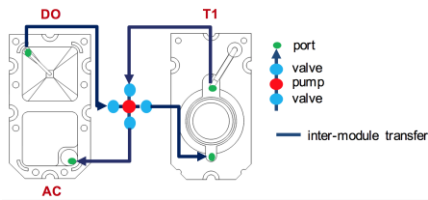
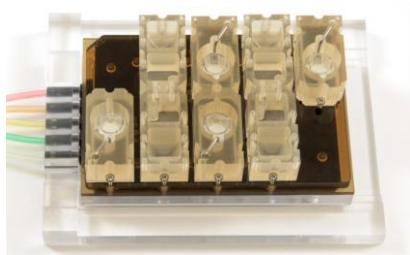


Jonathan Coppeta, Brett Isenberg, Jeff Borenstein
Draper Labs



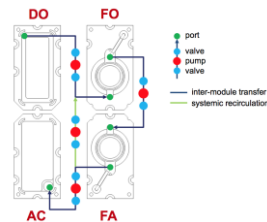
Microfluidic Systems

SOLO-MFP™



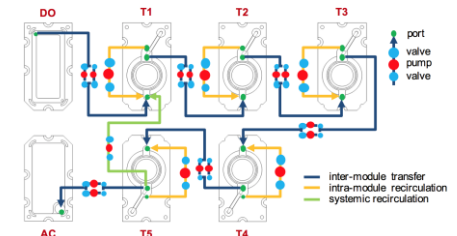
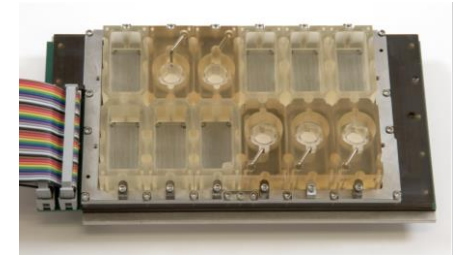
- Single tissue
- $N = 4$

DUET-MFP™



- Two tissue interactions
- Recirculation optional
- $N = 1$

QUINTET-MFP™



- Up to 5 tissues
- Recirculation
- $N = 1$

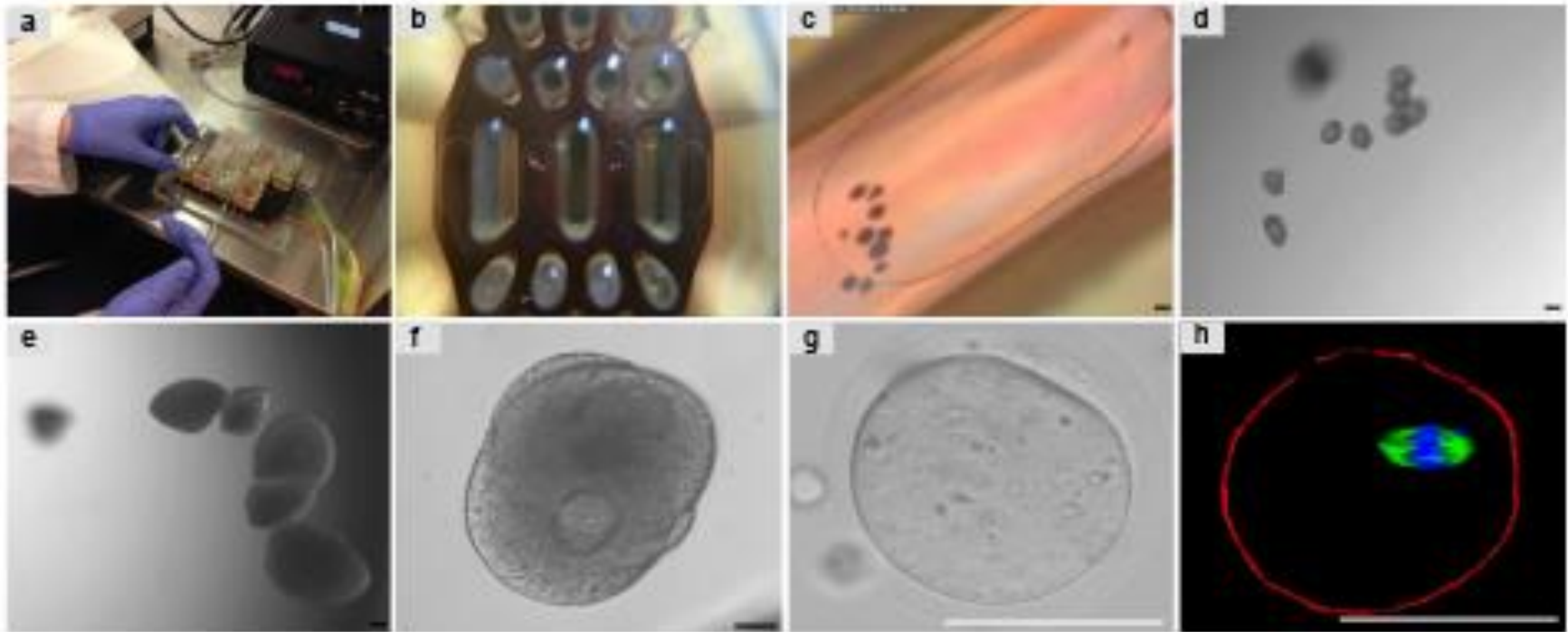
Microfluidic Follicle Culture



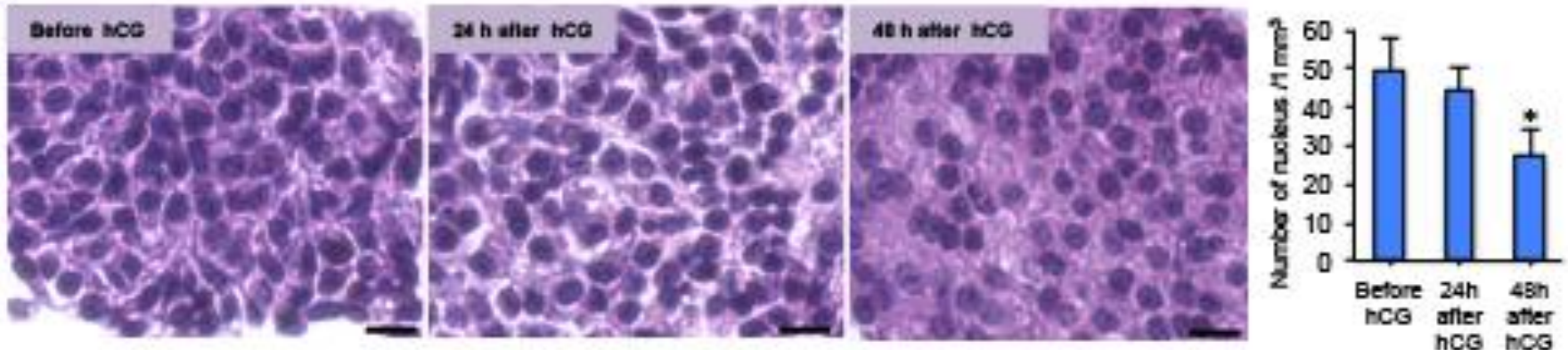
Imaging

Solo-MFP™ Supports 28 Day Follicle Function

A



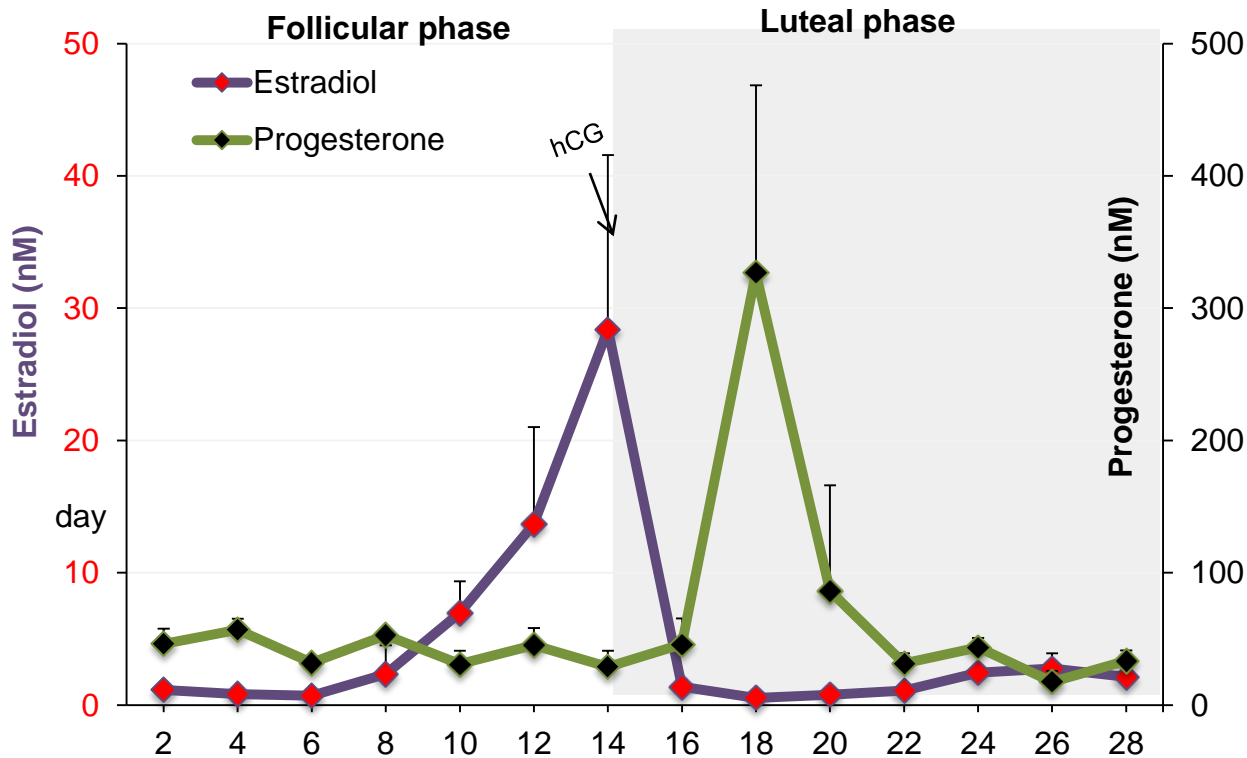
B



C

D

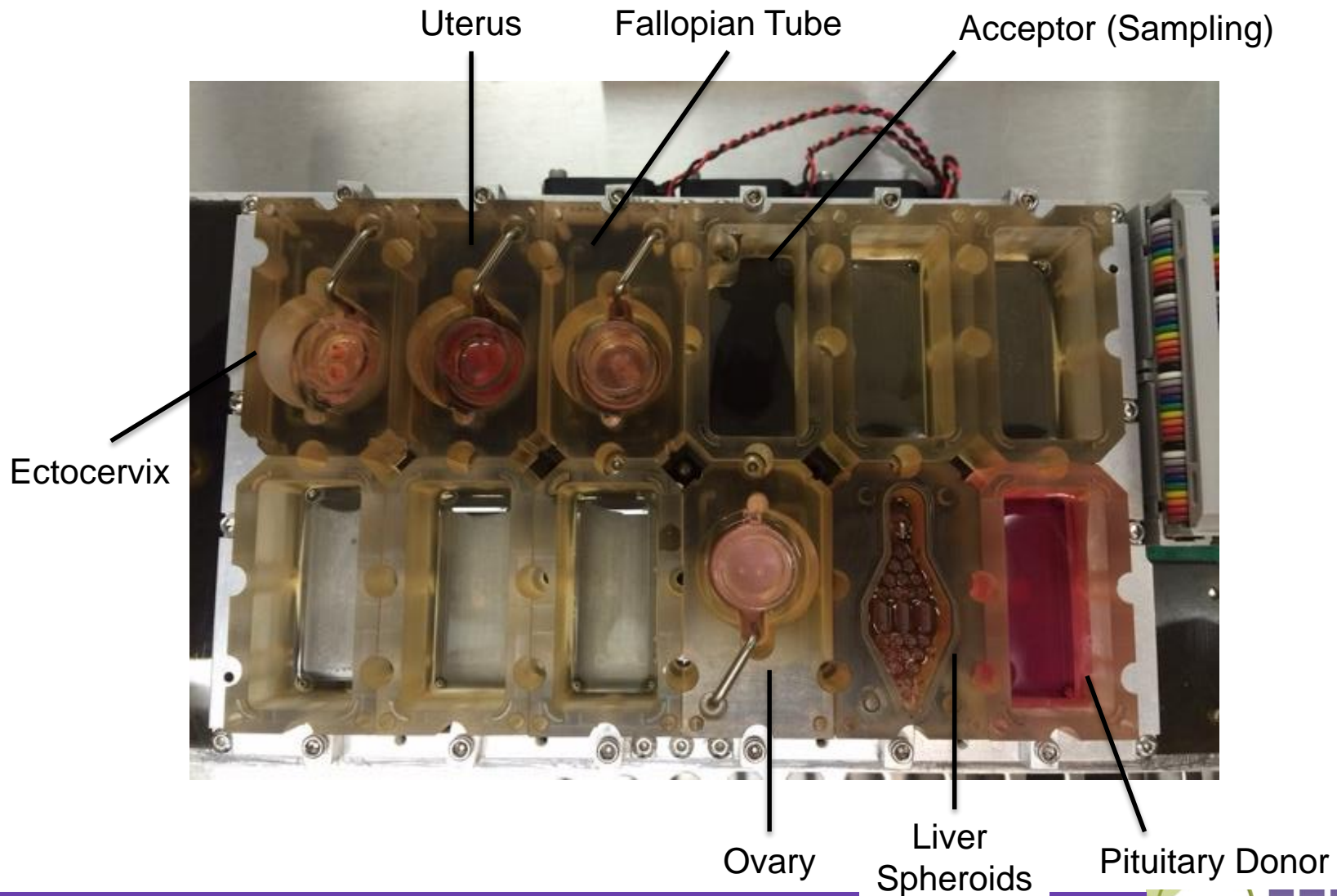
Microfluidic Follicle Culture



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

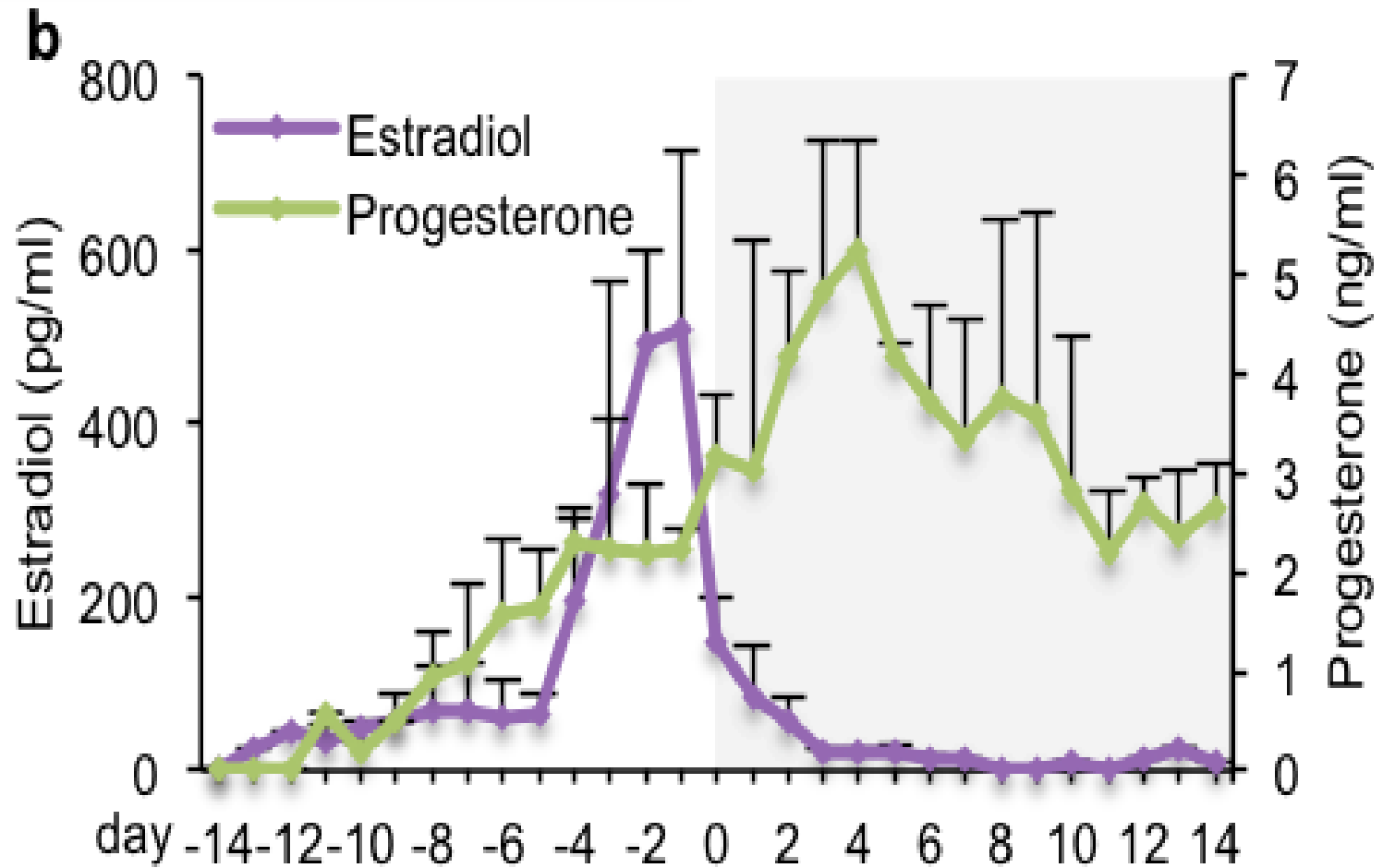
Operator Training, Stable Flow, Sampling

EVATAR – Ovarian Cycle in a Dish

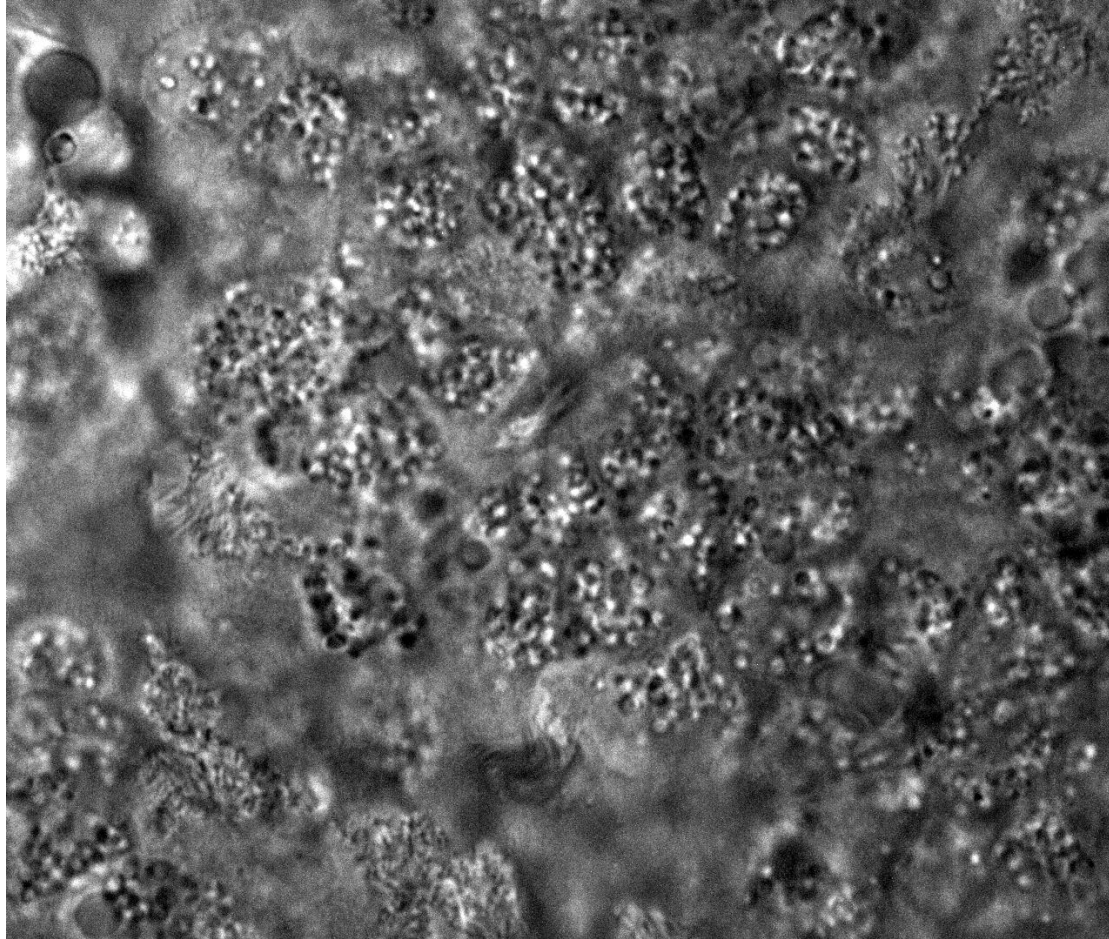


Xiao et al, *Nature Commun*, 2017.





Evatar™ Quintet-MFP™ Fallopian Tube Functioning



Xiao et al, *Nat Commun*, 2017.

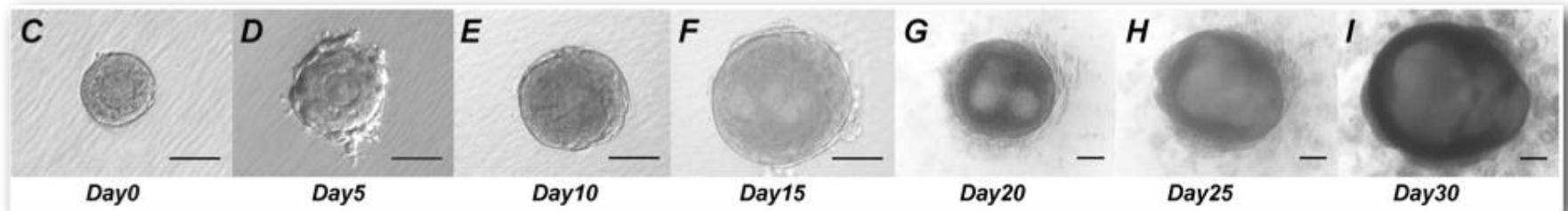
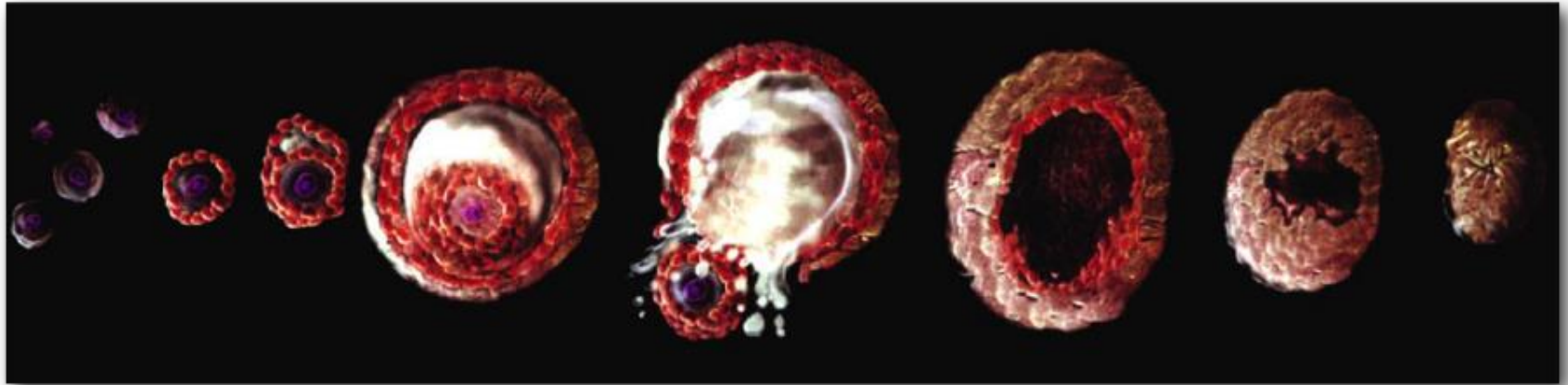


Reproductive tract physiology seems complicated...
But it is an integrated system with functional hallmarks
that can be modeled *in vitro*

Personalized Drug Testing Toxicology Testing Signaling Pathways Integrated Cell Biology



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

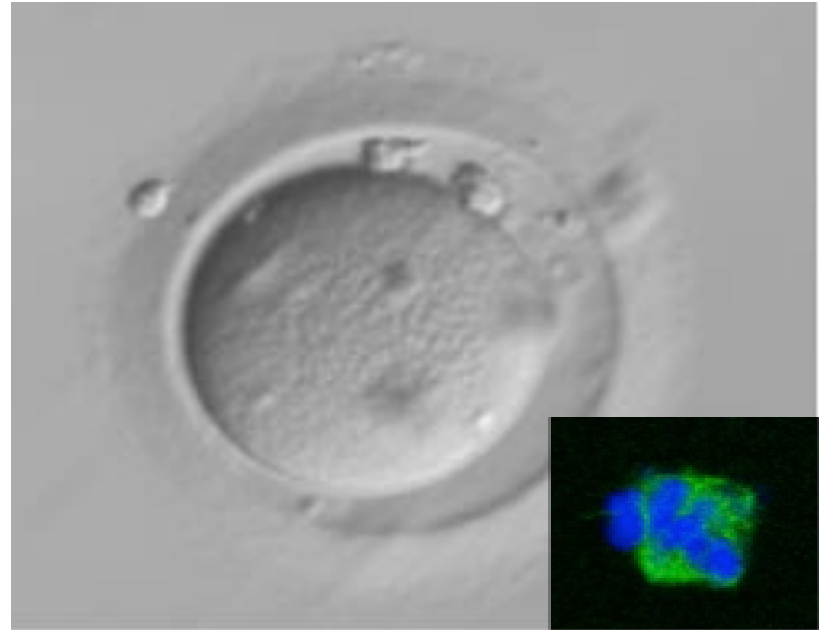


Grow - Secrete Hormones - Differentiate
Egg Matures - Ovulatory Mechanics - Connections
Live, Healthy Births in Mice
Architecture, Environment and Hormones

eIVFG Matured Human Oocytes

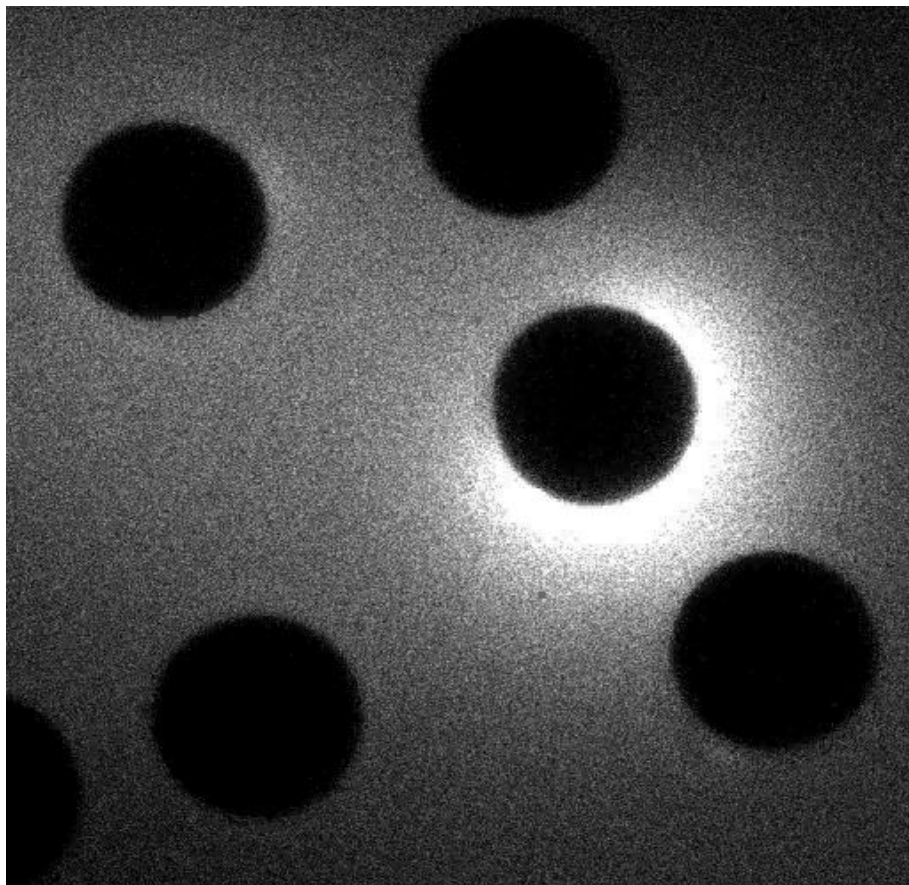


44 patients; 65 follicles; 4 MII



National Center for Translational Research in Infertility
NICHD P50

What Makes a Good Egg?



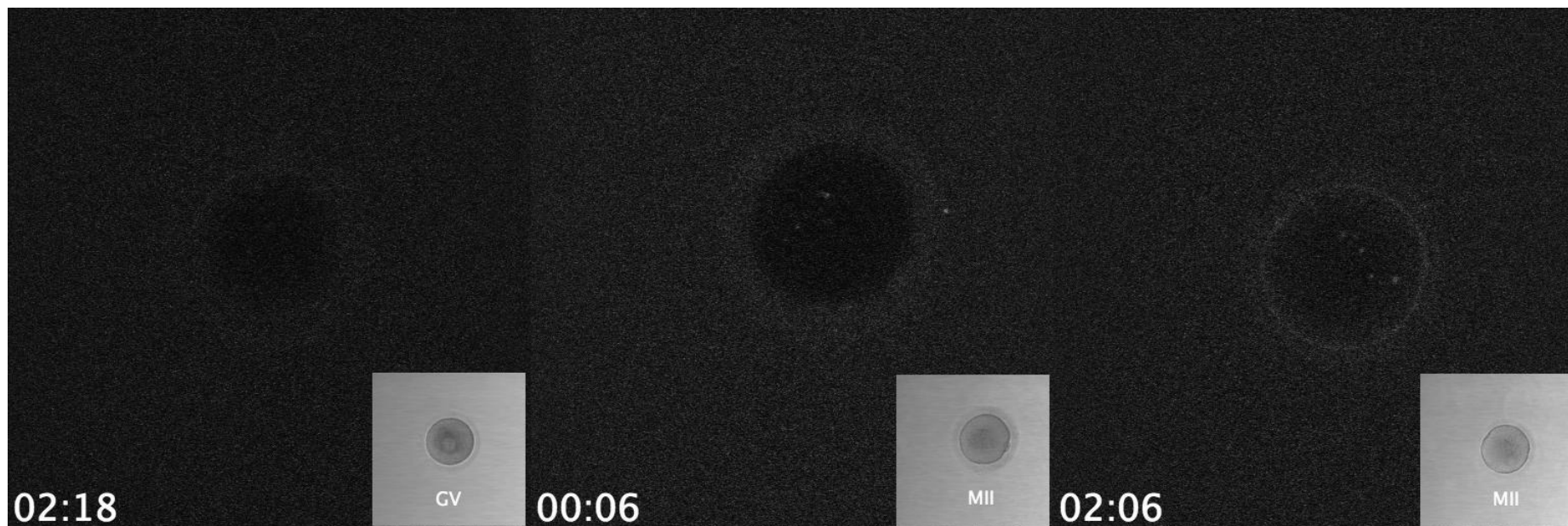
Kim, Bernhardt, Kong, Duncan, Que, Zhang, O'Halloran and Woodruff ***Nature Chemistry; Nature Chemical Biology; Scientific Reports*** (2009-present)



Francesca Duncan, Ph.D.
Assistant Professor
Northwestern University



Zinc is only released from mature, health human eggs

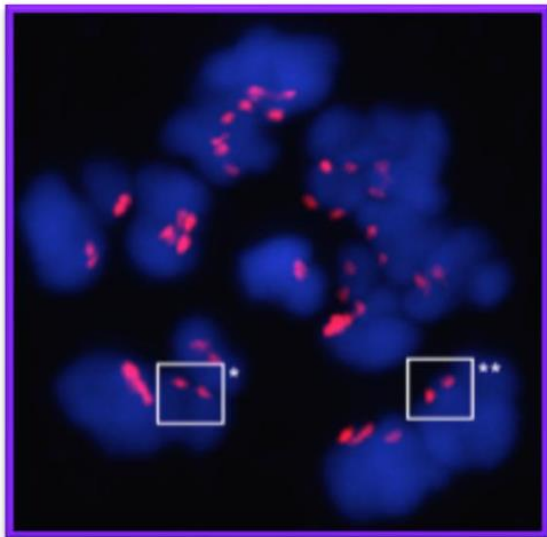


The zinc spark is an inorganic signature of human egg activation

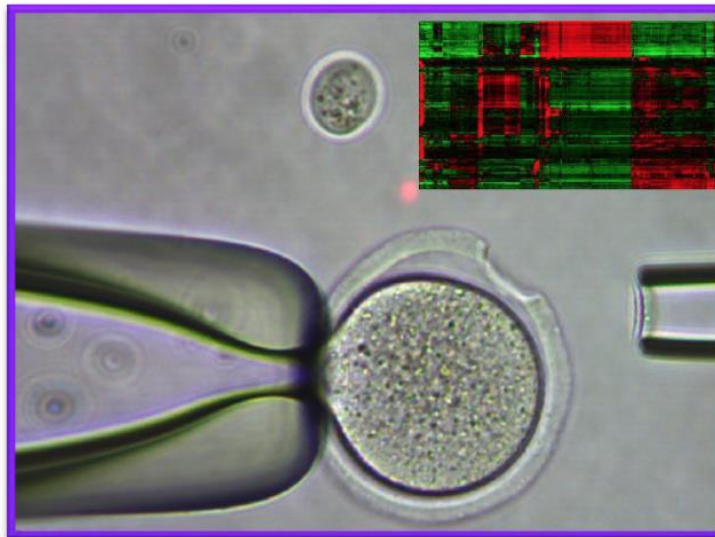
Francesca E. Duncan, Emily L. Que, Nan Zhang, Eve C. Feinberg,
Thomas V. O'Halloran, Teresa K. Woodruff* *Scientific Reports*, 2016

DISCOVER Magazine – Top 100 Discoveries of the Year

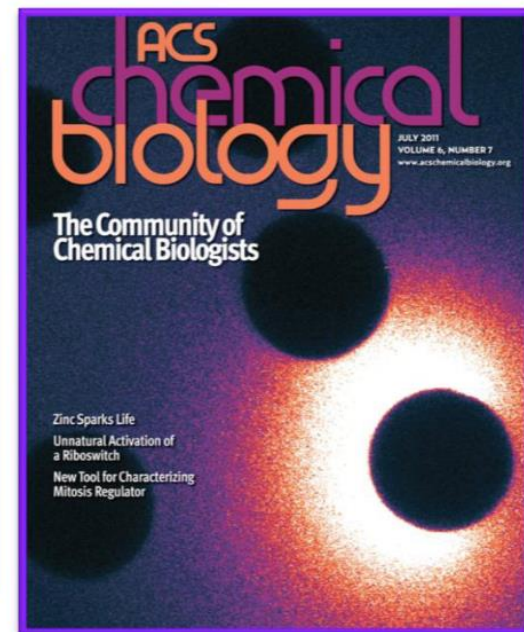
What makes a good egg?



Chromosome
number
and Structure

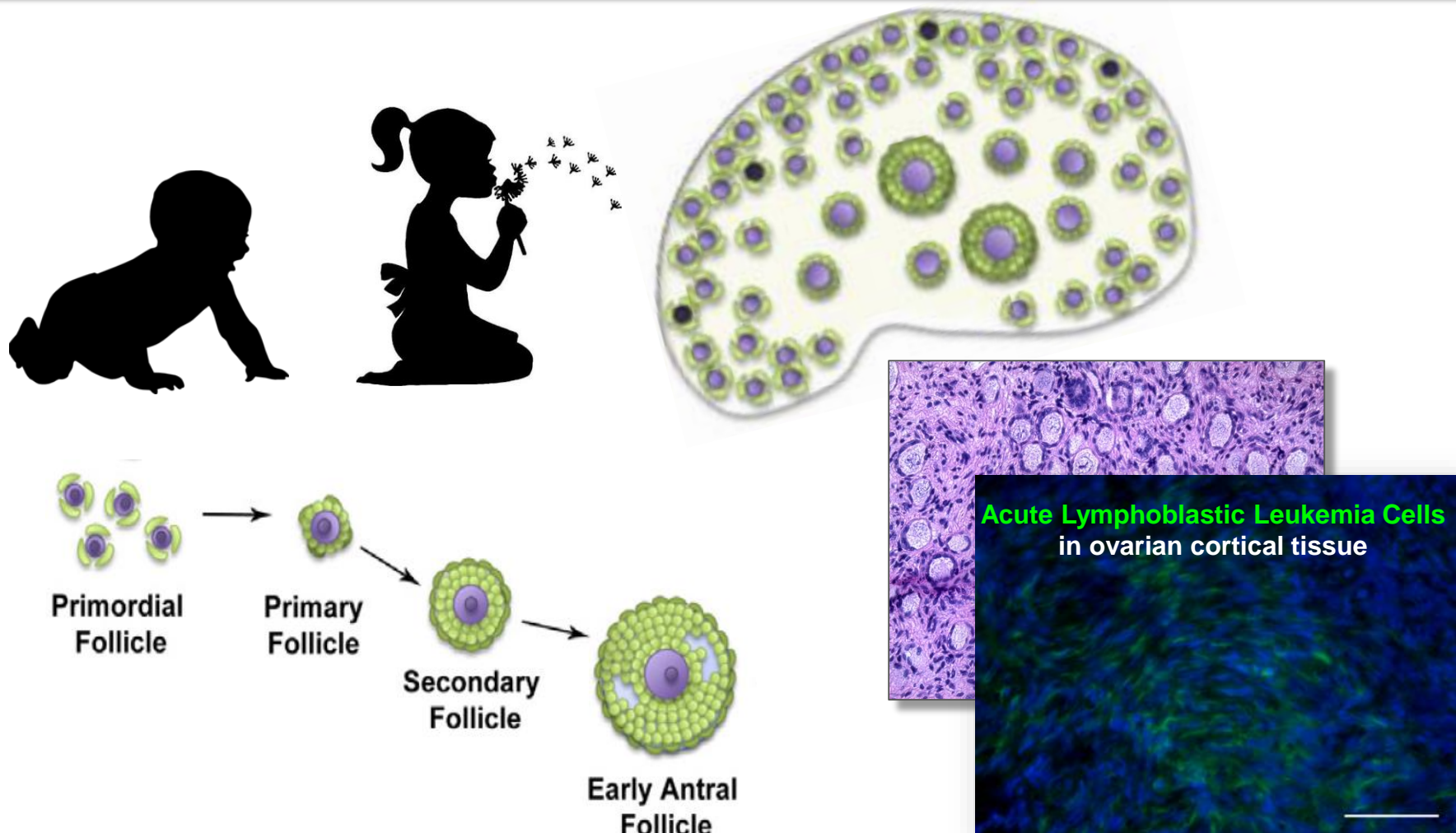


Oocyte-specific
gene expression



Zn exocytosis
at fertilization

Fertility Needs in Pediatric Cancer Patients



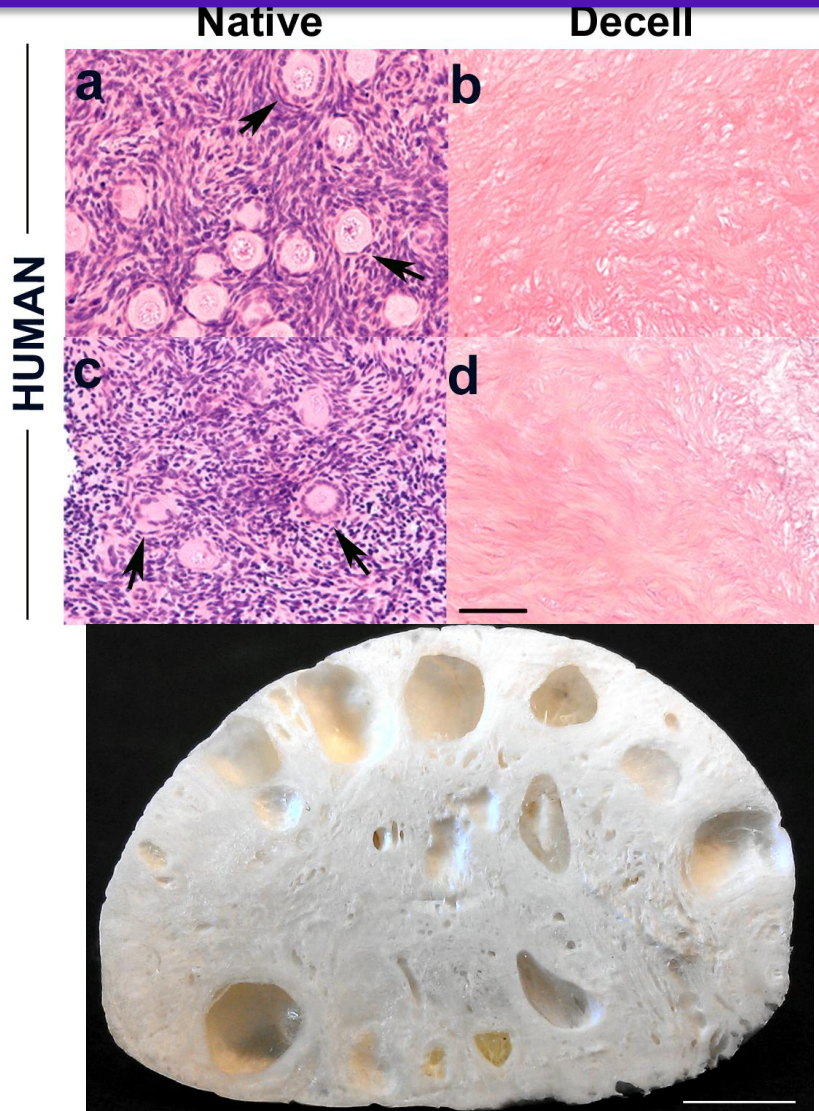
Ovarian cortical tissue from NPC participants;
Scale bar = 50 μ m Laronda, et al. (2015) Biomaterials

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

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

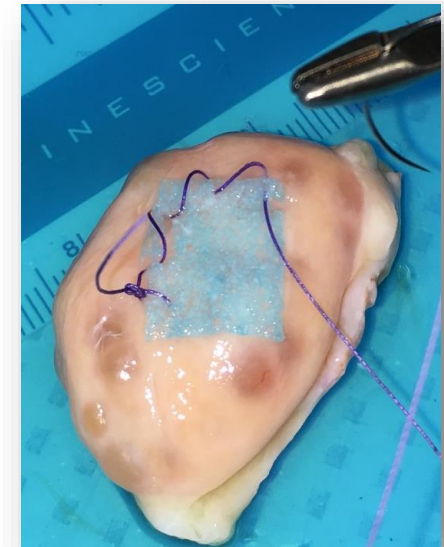
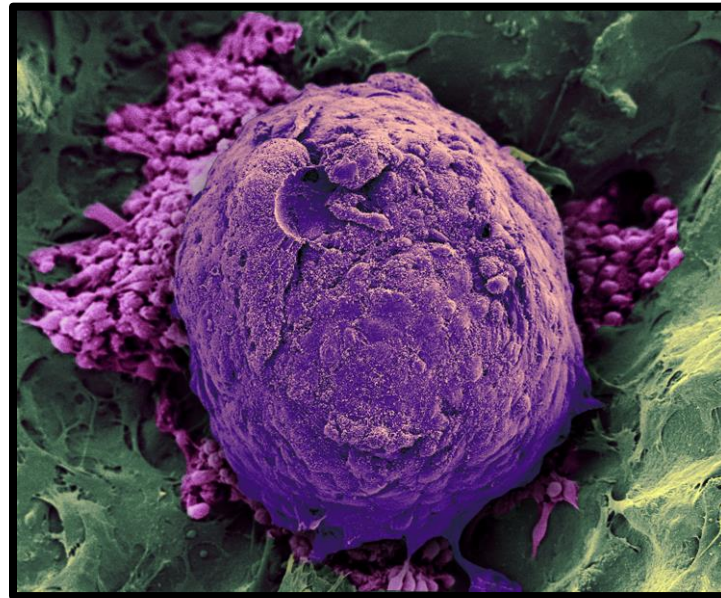
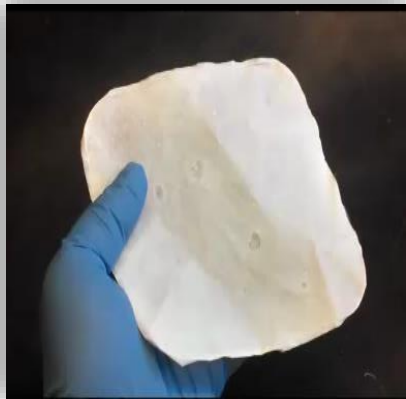
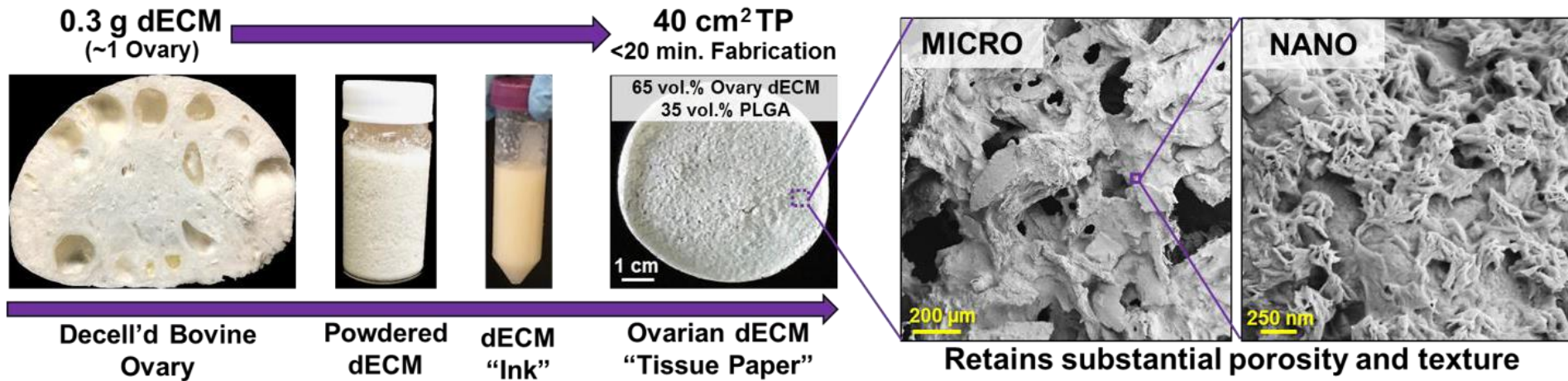


Decellularized Ovary for Bio-active Scaffold

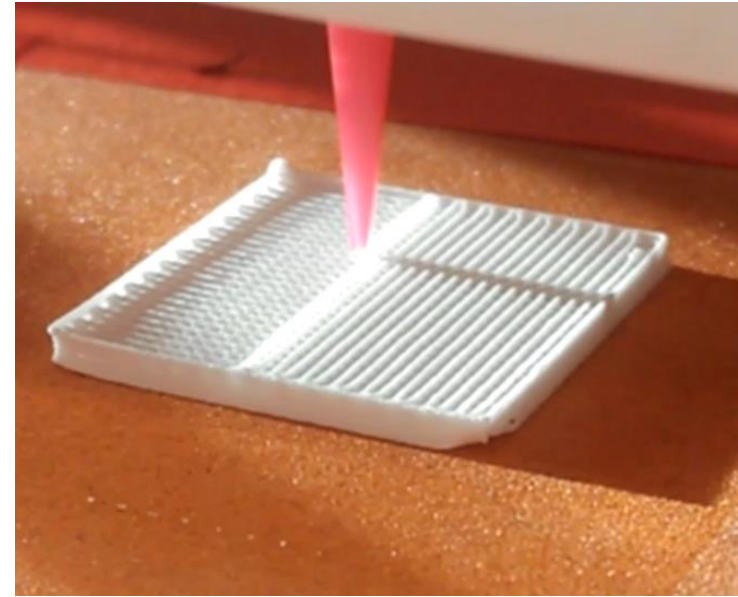
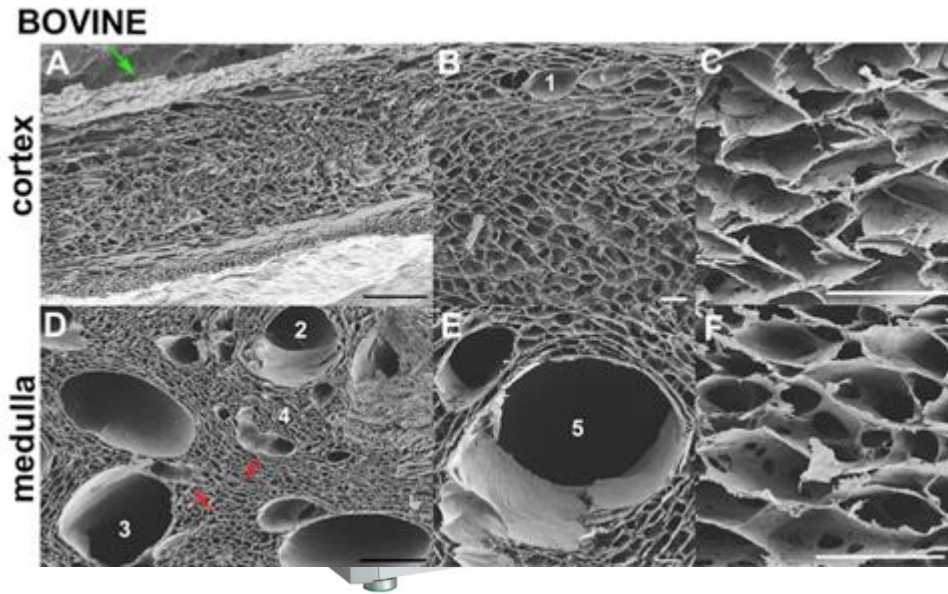


Monica Laronda, Ph.D.
Burroughs Wellcome Career Awardee
Assistant Professor, Dept Pediatrics, NU

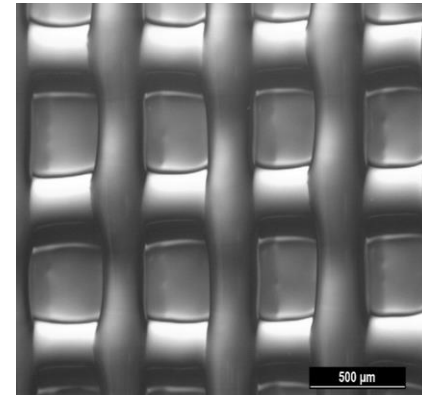
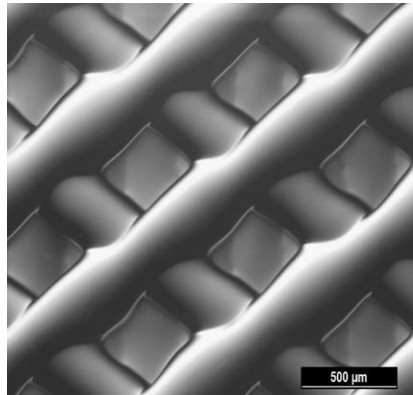
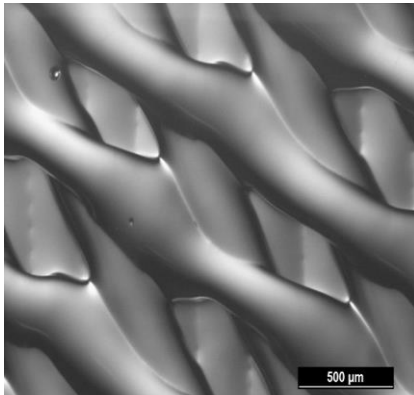
Bioinspired design of structural ECM as organ scaffolds



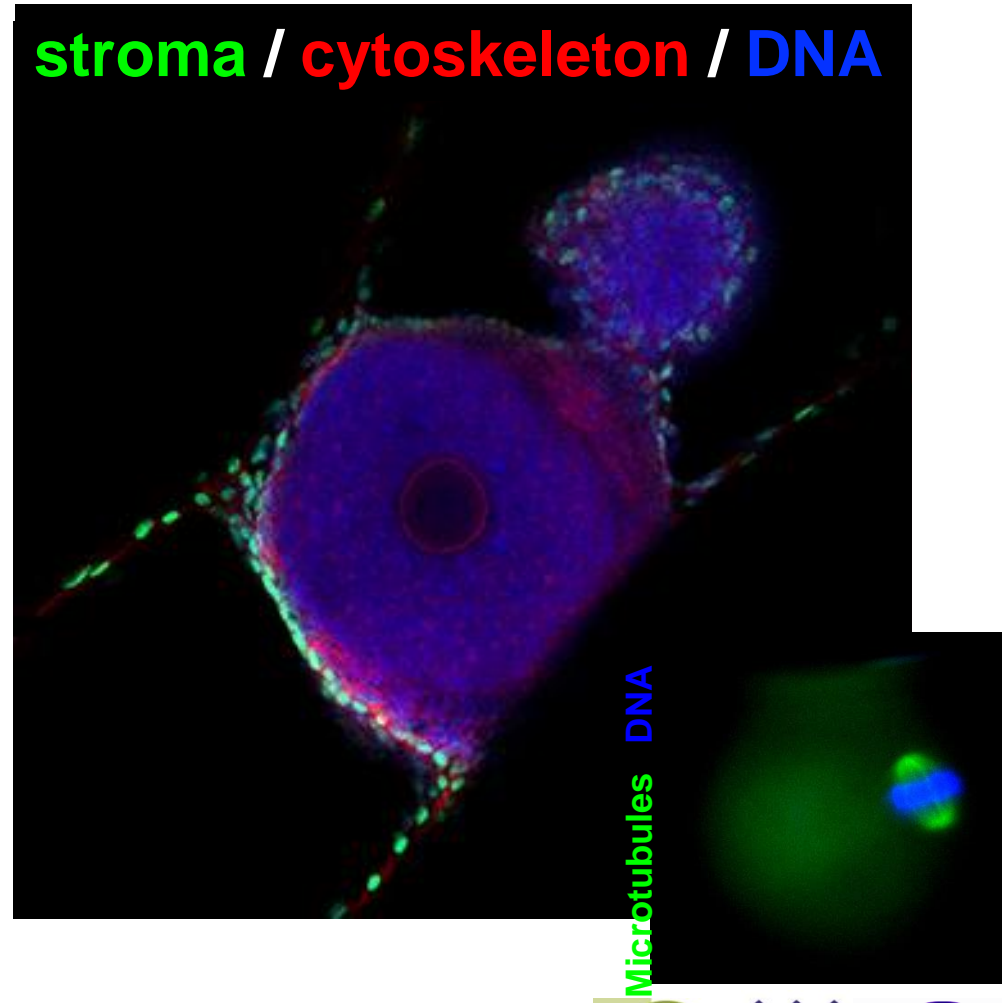
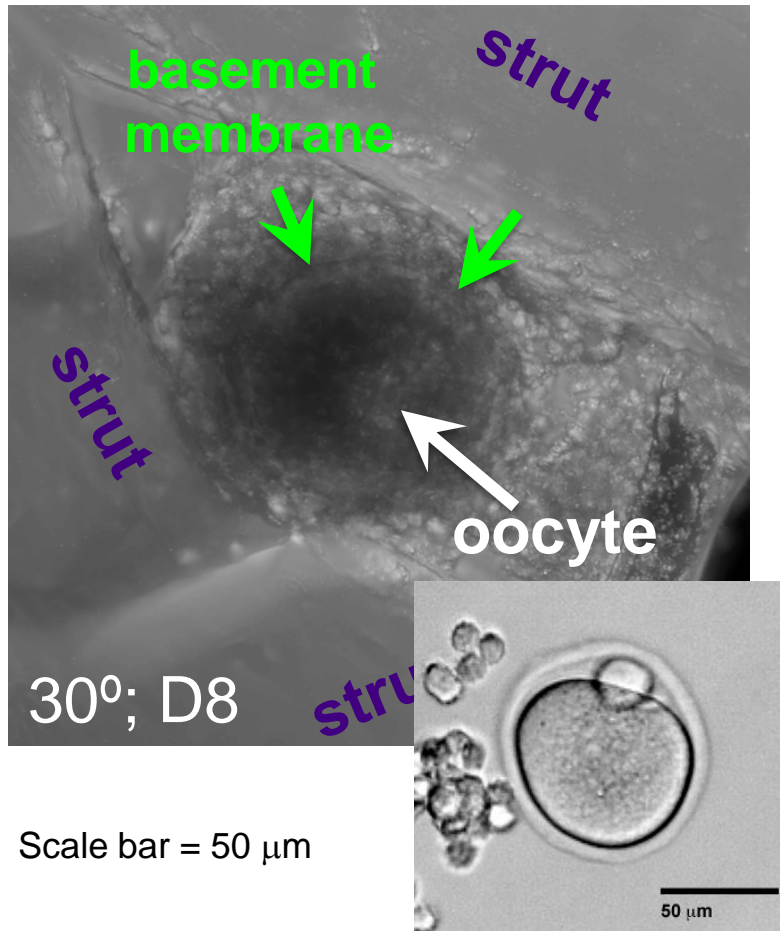
Bioinspired design of structural ECM as organ scaffolds



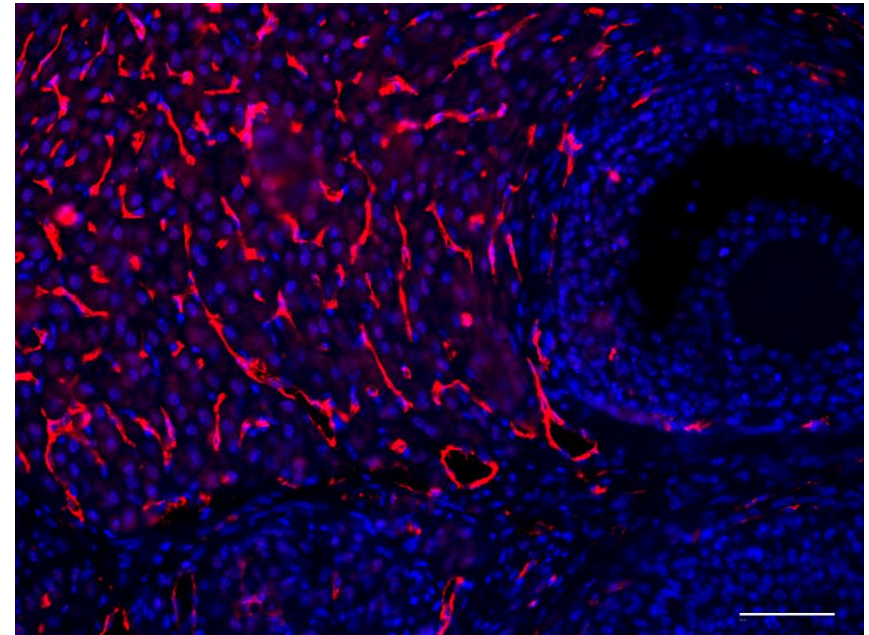
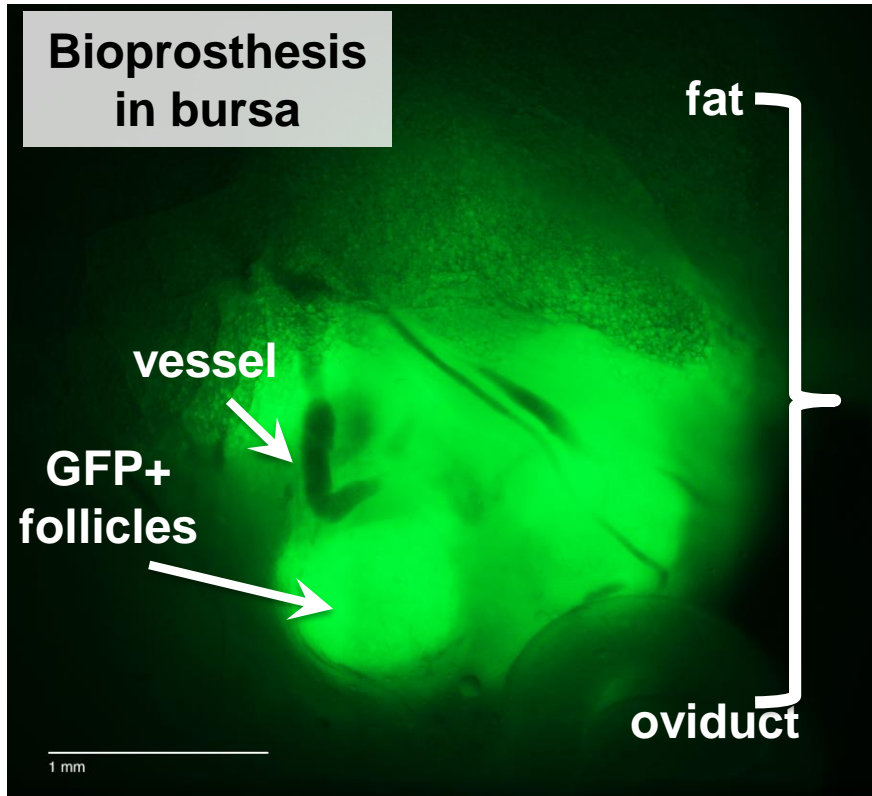
30° advancing angle 60° advancing angle 90° advancing angle



Bioinspired Scaffold Design –Follicle Development and Oocyte Maturation



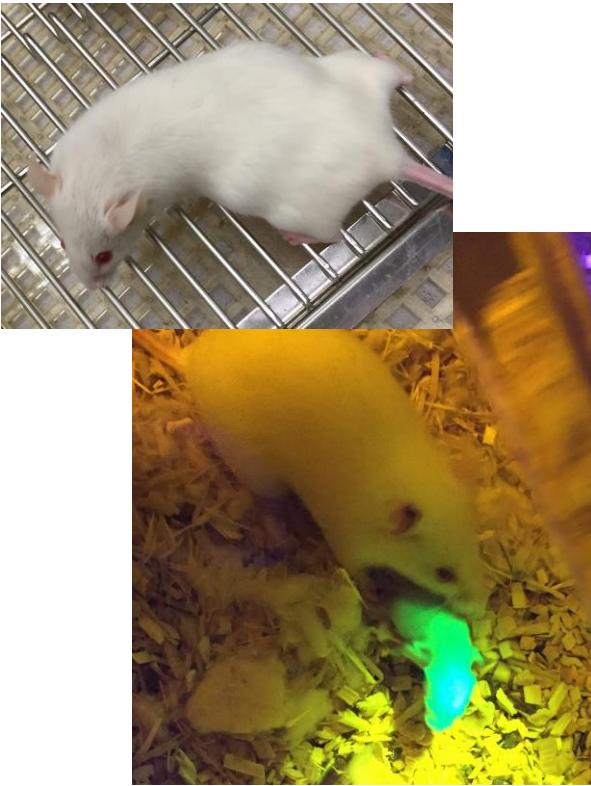
Bioinspired Scaffold Design – Soft Tissue Transplant



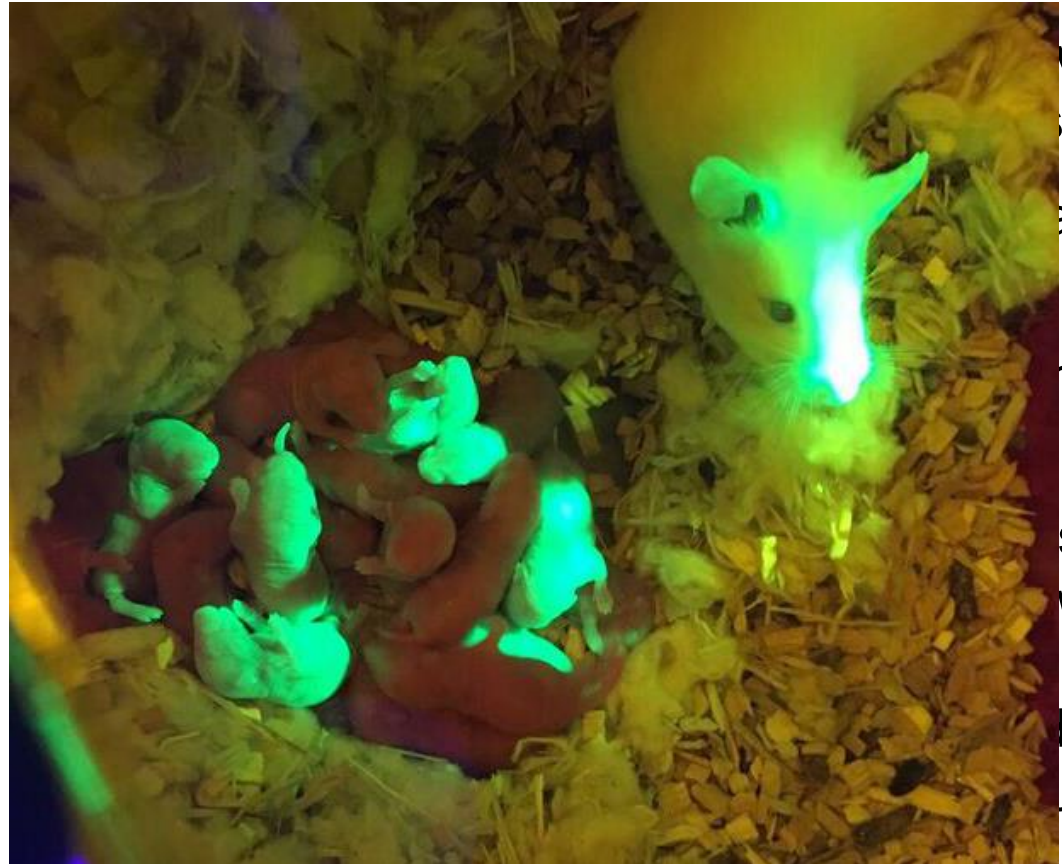
PECAM **DNA**

Live Birth from Ovarian Bioprothesetic Transplant

(first soft organ transplant)



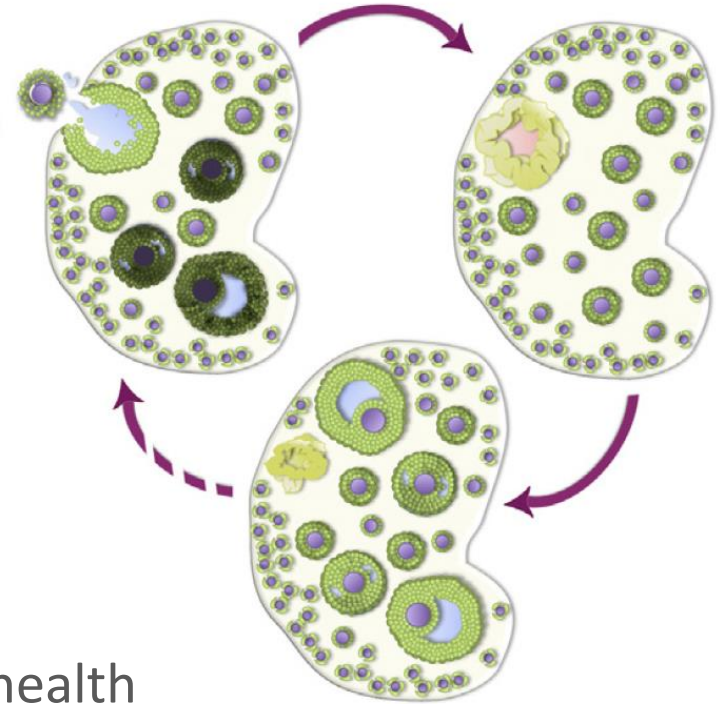
Transplant recipient (EGFP-)
with EGFP+ pup



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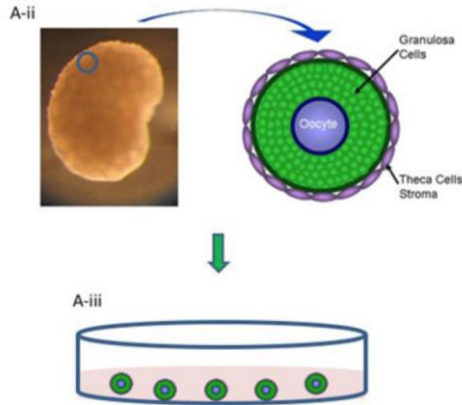
Fertility Needs in Pediatric Cancer Patients

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



Engineering the Reproductive Axis

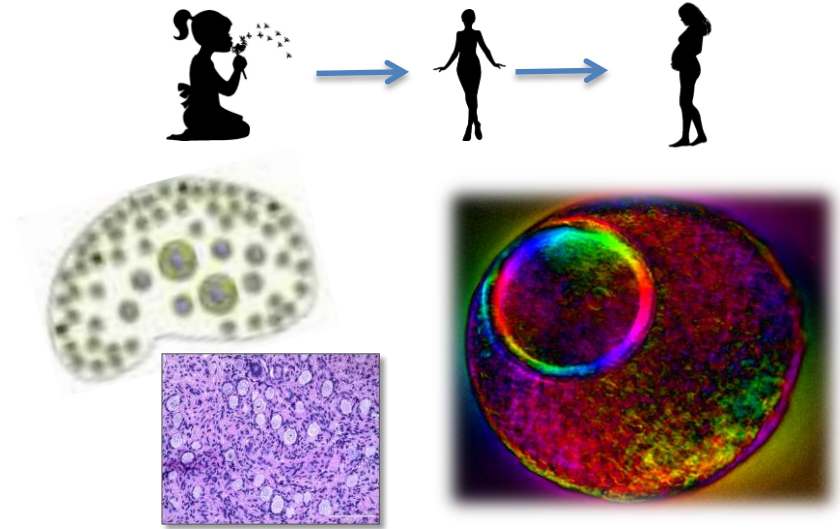
Follicle Maturation in a Dish



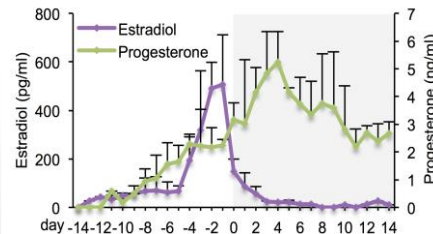
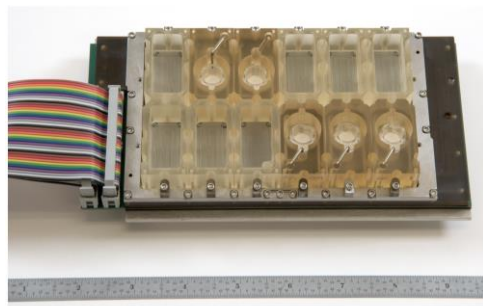
NUBorn & NUAge



Oncofertility Solutions



Engineered Reproductive Tract

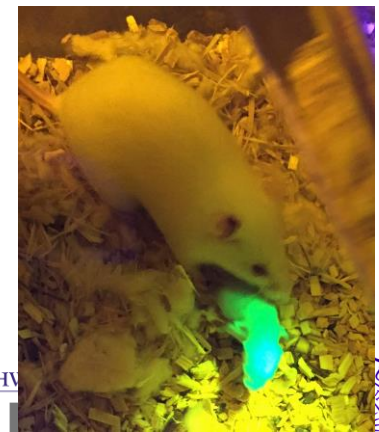
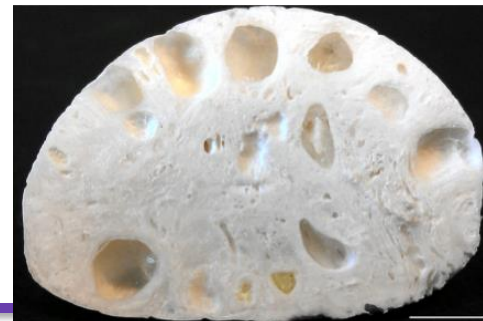


MFP-Ovulation



Artificial Ovary

Decellularized Ovary



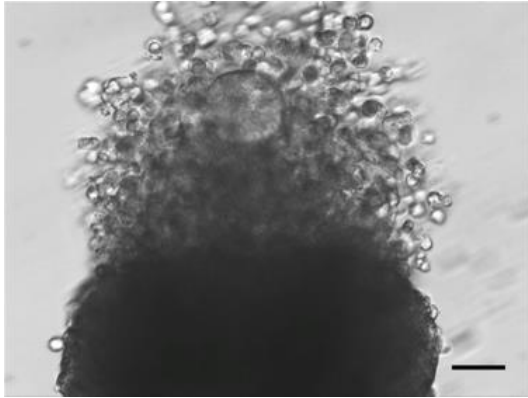
Oncofertility 2017



- ✓ 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



Bench to Bedside

NATIONAL
PHYSICIANS
COOPERATIVE

 the
Oncofertility®
Consortium
www.oncofertility.northwestern.edu

GLOBAL
ONCOFERTILITY
NETWORK

Thank you!



Funded by:
Oncofertility Consortium
NIH/NICHD: P50HD076188

Microfluidic Menstrual Cycle
NCATS/ORWH/NIEHS: UH3TR001207

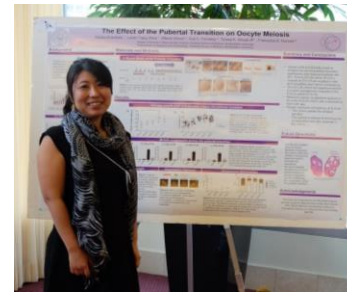
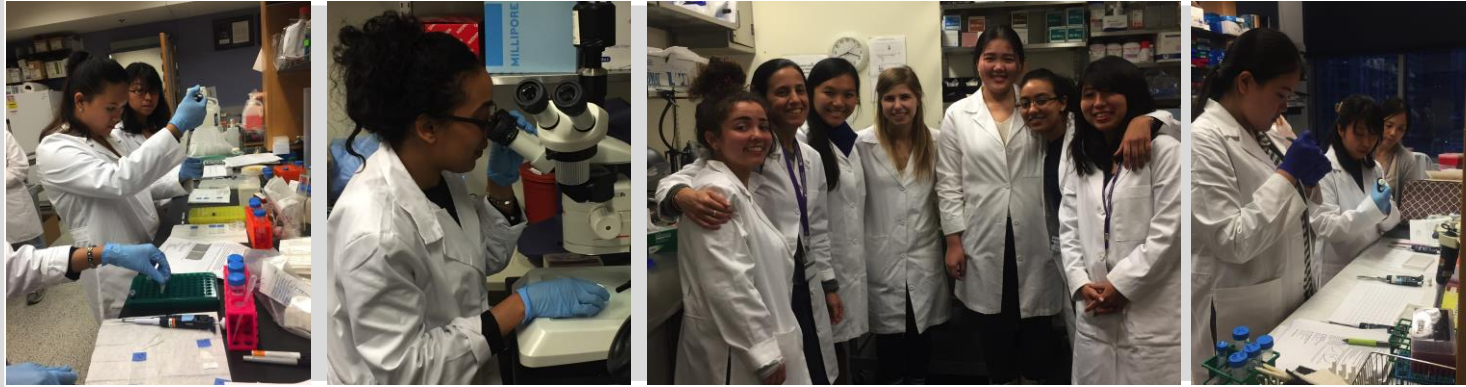
Zinc Spark
NIGMS: R01GM115848; Keck Foundation;
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Master of Science Reproductive Science and Medicine

A Degree Program Focusing on Human Reproductive Health



- Complete foundational and professional development courses
- Train with CRS leaders
- Engage in the Center for Reproductive Science activities

Information and application: <http://www.crs.northwestern.edu/>

Application deadlines: January 19, 2018 and April 30, 2018

INQUIRIES:

Repro-masters@northwestern.edu

Northwestern
THE GRADUATE SCHOOL

