Engineering Reproduction

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Preservation of Fertility After Cancer

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

Woodruff *Nature Medicine* 2009;
Gradishar, Smith, & Woodruff, *JAMA Oncol*, 2016
Options for Women

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

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

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 μm; National Physicians Cooperative
Laronda, et al. (2015) Biomaterials
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

Encapsulated In Vitro Follicle Growth (eIVFG)

Lonnie Shea, Ph.D.

Woodruff and Shea, 2000-present
Encapsulated In Vitro Follicle Growth (eIVFG)

Two somatic cell compartments

- DNA
- StAR

- DNA
- Inhibin α

Theca-like

Granulosa cells

unpublished

Follicles produce steroid hormones

Xu et al, Human Repro. 2009
Encapsulated *in vitro* follicle growth systems in basic reproductive research

- **Cow**
- **Dog**
- **Rhesus macaque**
- **Baboon**
- **Human**

**Follicle growth**

**Eggs & embryos**

**Eggs**

**Stage IV oocytes & eggs**

Duncan, 2016

Xiao *et al*, 2017

Xu *et al*, BOR, 2009; Xu *et al*, HR, 2011; Xu *et al*, HR, 2013

Xu *et al*, BOR, 2011

Xu *et al*, HR, 2009

Xu *et al*, unpublished
In Vitro Ovulation

Skory, Xu, Shea and Woodruff, Human Reprod. 2015
96% rupture (n=70)
In Vitro Ovulation and Luteinization

Skory, Xu, Shea and Woodruff, Human Reprod. 2015
eIVFG Produces MII Eggs and Supports Live Birth


Shea and Woodruff, Tiss Eng 2006
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
Shuo Xiao, Ph.D. Postdoc 2013-2016
Assistant Prof USC

Hunter Rogers, Graduate Student

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

FemKube Image Integration: Mingyang Jiang
Dino-Lite AM4815ZTL
Solo-MFP™ Supports 28 Day Follicle Function
Microfluidic Follicle Culture

Estradiol (nM) vs. Progesterone (nM)

Follicular phase

Luteal phase

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

Operator Training, Stable Flow, Sampling
EVATAR – Ovarian Cycle in a Dish

Evatar™ Quintet-MFP™
Fallopian Tube Functioning

Reproductive tract physiology seems complicated…
But it is an integrated system with functional hallmarks
that can be modeled \textit{in vitro}

Personalized Drug Testing
Toxicology Testing
Signaling Pathways
Integrated Cell Biology

Woodruff, Kim, Burdette, Pavone, Draper et al 2012-present
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
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

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

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

Jakus, Laronda, … Woodruff and Shah, 2017 in press
Bioinspired design of structural ECM as organ scaffolds


SEM by Adam Jakus
Bioinspired Scaffold Design –Follicle Development and Oocyte Maturation

- 30°; D8
- basement membrane
- strut
- oocyte

stroma / cytoskeleton / DNA

Scale bar = 50 μm
Bioprosthesis in bursa

- Fat
- Vessel
- GFP+ follicles
- Oviduct

PECAM DNA

Transplant recipient (EGFP-) with EGFP+ pup

Live Birth from Ovarian Bioprothesetic Transplant

(first soft organ transplant)

✓ 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

Oncofertility Solutions

NUBorn & NUAge

Engineered Reproductive Tract

Artificial Ovary

Decellularized Ovary

MFP-Ovulation
We seek solutions. We don’t seek - dare I say this - just scientific papers any more.

Steven Chu, March, 2009
Bench to Bedside
Thank you!

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Draper Labs
Woodruff Lab Past and Present
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

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