Oncofertility: From Bench to Bedside to Babies

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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
Funded by NICHD: P50HD076188
National Physicians Cooperative
An Infrastructure Partnering Medicine and Science

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

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

oncofertility.northwestern.edu
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


Funded by NICHD: P50HD076188 Pilot
Tissue Cryopreservation for Patient Use and Research

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

NATIONAL PHYSICIANS COOPERATIVE

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

Encapsulated In Vitro Follicle Growth (eIVFG)

Woodruff and Shea, 2000-present

Lonnie Shea, Ph.D.

NATIONAL PHYSICIANS COOPERATIVE

GLOBAL ONCOFERTILITY NETWORK
Encapsulated In Vitro Follicle Growth (eIVFG)

Successful Thesis Defense!

Pangas et al, Tiss. Eng. 2003
In Vitro Ovulation

In Vitro Ovulation and Luteinization

Mechanisms of Ovulation

Gates Foundation
eIVFG Produces MII Eggs and Supports Live Birth


Shea and Woodruff, Tiss Eng 2006
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

Woodruff, *PNAS* 2014
Laronda et al. *Stem Cell Research and Therapy*, 2014
Microfluidic Follicle Culture

Funded by NIEHS/ORWH/NCATS/NICHD

FemKube Image Integration: Mingyang Jiang
Dino-Lite AM4815ZTL
Microfluidic Follicle Culture

Follicular phase

- Estradiol
- Progesterone

Luteal phase

hCG

- 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\textsuperscript{TM} Quintet-MFP\textsuperscript{TM}
Fallopian Tube Functioning

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

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
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.”

Tingen, Rodriguez, Campo-Engelstein, Woodruff *Science*, 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

Acute Lymphoblastic Leukemia Cells in ovarian cortical tissue

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

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

Decell’d Bovine Ovary

Powdered dECM

dECM “Ink”

Ovarian dECM “Tissue Paper”

0.3 g dECM (~1 Ovary)

40 cm² TP

<20 min. Fabrication

MICRO

NANO

Retains substantial porosity and texture

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


SEM by Adam Jakus
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

Artificial Ovary

MFP-Ovulation

Decellularized Ovary
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 Fertoprotecitives
- In Vitro Follicle Maturation
- Designer Ovarian Bioprosthetics
- Eliminate the Field

I have been taught that the way of progress is neither swift nor easy.

Marie Curie, 2021
Bench to Bedside
Thank you!

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Zinc Spark
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Draper Labs
Woodruff Lab Past and Present
Thank you!

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