Oncofertility: The Preservation of Fertility for Cancer Patients

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Research interests

- Characterize negative feedback endocrine loops controlling follicle development

- Understand the fundamentals of follicle selection and recruitment

- Develop methods to mature follicles in vitro and in vivo

...exploring and expanding options for the reproductive future of cancer survivors
Goals

- **Explain** patterns of follicle recruitment

- **Provide new angles on idiopathic follicle disease**

- **Extend option menu** to young women, teens and girls who are at risk for ovarian failure:
  - Iatrogenic
  - Age
  - Genetic
  - Environmental
  - Endangered and threatened species
Goals

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Preservation of Fertility After Cancer

- Life preserving treatments
  - Chemotherapy
  - Radiation treatment
  - Surgery

- Can threaten fertility
Who is at risk?

- More than **1.4 million** new cancer patients are diagnosed in U.S. annually
- 10 million new cases diagnosed globally
- **10%** are in their reproductive years (up to age 45)
- Approximately **11%** of breast cancer patients are diagnosed under the age of 40

*West et al, Pediatric Cancer 2009*
*Jeruss and Woodruff, NEJM, 2009*
Options for women and girls

Non-intervention and/or Non-biological
- Natural Pregnancy
- Donor egg
- Adoption

Interventional
- Embryo/Egg Bank
- Oophoropexy
- Conservative Surgery
- Ovarian Tissue Cryopr.
- Surrogacy

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NEJM, Jeruss and Woodruff, 2009
The Oncofertility Program at Northwestern: 2009

4000 new cancer patients seen
300 providers/patients called our FERT Line
150 had a consultation for fertility preservation
75 had a fertility preservation intervention

53 Embryo Banking
15 Oocyte Banking
7 Ovarian Tissue Cryopreservation
Tissue Transplant in U.S.

Successful - live, healthy offspring
Provision of endocrine support
Slow freeze tissue maintains adequate primordial/primary follicle health
Progress in *in follicle* maturation (IFM)

*Li et al, Endocrinology, 1995*
*Woodruff, et al, BOR, 1993*

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Perhaps the structural context matters to developmental competence

Woodruff et al, Science, 1988

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Biomaterial Design: Alginate

- Encapsulates viable cells
- Gelling mechanism is reversible
- Gels are highly porous
- Minimal interactions with mammalian cells

β-D-Mannuronic acid
α-L-Guluronic acid

Lonnie Shea, Ph.D.
Dept. Chem/Biol. Engineering

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Encapsulation methods

Min Xu, et al.

50 mM CaCl$_2$

Pangas et al., Tissue Eng. 2003
Kreeger et al., BOR, 2005; Biomaterials, 2006

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The follicles grow...


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...and develop two differentiated compartments.

Xu, unpublished

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Wednesday, December 16, 2009
2-Dimensional Culture vs. 3-D Culture
2-Dimensional Culture vs. 3-D Culture
2-Dimensional Culture vs. 3-D Culture
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2-Dimensional Culture vs. 3-D Culture

A. GC
   CG
   ZP
   Oocyte

B. ZP
   Arrow
   Oocyte
The murine follicles synthesis steroids...

Living follicle stained for 3B-HSD activity

West et al., Biomaterials, 2007
West et al., BOR, 2008

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...and form an antrum.

West et al., BOR 2008
...and form an antrum.

West et al., BOR 2008

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The follicles respond to hCG by expelling an expanded cumulus-oocyte complex…

Barrett, unpublished
...and the somatic cells luteinize.

Hormone Analysis

Sarah Kiesewetter, Jen Jozefik, Tyler Wellington, unpublished

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The oocytes can be fertilized...

Xu, et al, BOR, 2006
Jin, et al, Fert Steril, in press

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...and the tissue engineered system supports live, healthy, reproductively competent offspring.

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**Xu, et al, Tiss. Eng.  2006**

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Can We Adapt the Engineered Mouse Follicle Maturation System to Human?

A  B  C  D
GOCs Collagen Transwell  Secondary Follicles Adhesive Substrate


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Differences between murine and primate follicles

- Size
- Time
- Significance of classic morphologic and biochemical hallmarks
- Environmental Cues
  - Physical - mechanical
  - Cell-Cell interactions - ECM docking proteins
  - Gas - oxygen need and availability
- Tissue acquisition
Fertility Preservation at Northwestern University (2007-2008)

88 patients chose Fertility Preservation options between May 2007 to May 2008

Options chosen:
- Embryo cryopreservation (33)
- Oocyte cryopreservation (5)
- Ovarian Tissue Cryopreservation (19)

Factors involved in patient decisions about options:
time to treatment, probability of success, partner status
Ovarian Tissue Cryopreservation at Northwestern University

19 patients enrolled between May 2007 to May 2008

Age range 16 to 40 (average 26 years)

Tissue Preparation for Long Term Storage and Donation to Research Team


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Human Follicle Growth


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Human Follicle Growth


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Human follicles develop...


Barrett, submitted

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Human follicles develop...

Barrett, submitted*

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The human follicles are functional...

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…and maintain TZPs and high quality GV.

Susan Barrett, Hum. Reprod. 2009, and unpublished
Exploring and expanding options for the reproductive future of cancer survivors.

National Physicians Cooperative
866-708-FERT (3378)

http://oncofertility.northwestern.edu/
www.myoncofertility.org

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In summary...

...exploring and expanding options for the reproductive future of cancer survivors

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Team Follicle

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Thank you!

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