

# REPRODUCTION MATTERS

A publication of the  
**Center for Reproductive Science**  
Northwestern University  
Evanston & Chicago

Winter 2005

## 25th Anniversary of Minisymposium

The 25th Annual Minisymposium on Reproductive Biology took place on October 18, 2004 at the Hilton Garden Inn in Evanston. Fourteen trainees gave oral presentations and 44 trainees gave poster presentations. In addition to presenters from Northwestern's Evanston and Chicago campuses, presentations were given by trainees from University of Illinois (Chicago and Urbana), University of Wisconsin (Madison and Whitewater), Loyola University, Rush University Medical Center, University of Chicago and University of Florida. This year's event boasted a record number of participants and attendees, making it the largest Minisymposium in the Center's history.

To celebrate the 25th anniversary of the Minisymposium, CRS invited five alumni guest speakers to present their perspectives and advice to trainees pursuing careers in reproductive biology. The alumni speakers were a welcome addition to the annual event.

The alumni speakers were: **Dr. Deborah DeManno**, Senior Research Investigator, TAP Pharmaceuticals, *Northwestern Postdoctoral Fellow and Research Associate: 1987-1994, Hunzicker-Dunn Lab*; **Dr. Rosemary Haggett**, Professor of Animal and Veterinary Science, West Virginia University, *Northwestern Postdoctoral Fellow: 1979-1982, Schwartz Lab*; **Dr. John Kirby**, Professor of Reproductive Biology, Director, Cell and Molecular Biology,



Dr. Neena Schwartz and Vice President for Research C. Bradley Moore

### Neena B. Schwartz Lectureship in Reproductive Science

The idea for the Minisymposium, a day-long event focused on providing trainees with an early opportunity to present their research, came primarily from Dr. Neena B. Schwartz, William Deering Professor Emerita of Biological Sciences. Dr. Schwartz is the founder and former Director of the Center for Reproductive Science.

To honor Dr. Schwartz on the occasion of the 25th annual Minisymposium, the Center for Reproductive Science named the keynote address the *Neena B. Schwartz Lectureship in Reproductive Science*. This year, **Dr. William F. Crowley Jr.**,



distinguished Professor of Medicine at Harvard Medical School and Massachusetts General Hospital gave the keynote address and received the inaugural lectureship award. The title of his address was "Understanding the Genetic Control of GnRH Secretion in the Human: Use of Clinical Models".

University of Arkansas, *Northwestern Postdoctoral Fellow: 1990-1992, Turek Lab*; **Dr. Cheryl Sisk**, Director, Neuroscience Program, Michigan State University, *Northwestern Postdoctoral Fellow: 1980-1982, Turek Lab*; **Dr. Eric Widmaier**, Professor of Biology, Boston University, *Northwestern Undergraduate and Graduate Student: 1975-1979, Campbell Lab*.

(\*\**Winners of the Constance Campbell Memorial award and more Minisymposium pictures - Page 2* )



CRS Director Dr. Kelly Mayo, NU alumni speaker Dr. Rosemary Haggett and Dr. Teresa Woodruff

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## From the Director...

It has been somewhat of a "silver anniversary" year for CRS, which recently celebrated its 25th Minisymposium in Reproductive Biology and its 25th year of funding for the NIH-sponsored Training Program in Reproductive Biology. Both of these special events are highlighted in this issue of Reproduction Matters. It was especially rewarding to have our former trainees visit campus and speak fondly about their "Northwestern years". We look with excitement to the next 25 years!

You may notice a new look and feel with this edition of the CRS newsletter. After many years with Northwestern and CRS, Mr. Mukhtar Rafiqi has retired. We thank him for his invaluable contributions and wish him well. Many of you will by now know Lise Jinno, our new CRS program assistant, and we welcome her to CRS. Among her many duties, Lise is the new production editor for the newsletter, and I am sure she will welcome your suggestions for further improvements or for newsworthy topics. Lise is also taking a significant role in the updating of the CRS website. If you have not visited recently, please take a look at the many new features (<http://www.northwestern.edu/research/crs/>). We welcome your suggestions for improvements and additions.

Finally remember - with growing concern about an increasing world population and a deteriorating environment --- reproduction matters!

Dr. Kelly Mayo

Director, Center for Reproductive Science

## CRS Welcomes Two New Members!

The two newest members to join CRS are **Chris Kuzawa, Ph.D., Anthropology** and **Xiaobin Wang, M.D., M.P.H., Sc.D., Pediatrics**. Both Chris and Xiaobin are actively involved in research and are at the forefront of their areas of expertise.

**Dr. Kuzawa's** work focuses on understanding human health as an outcome of evolutionary and developmental processes. His primary work in the Philippines explores the long-term developmental and health implications of fetal and maternal nutrition during pregnancy (in collaboration with Linda Adair of the University of North Carolina, Chapel Hill and Thomas McDade of Northwestern). He has used ultrasound data to monitor fetal growth responses to stressors, such as maternal smoking during pregnancy (in collaboration with Michelle Lampl, Emory University, and Philippe Jeanty, Women's Health Alliance, Nashville). He has also written on the evolutionary significance of brain energetics and human 'baby fat' in early human development, and historical and evolutionary perspectives on disease change in human populations.

**Dr. Wang** is a molecular epidemiologist whose work unites molecular biology, genetics, clinical medicine, and epidemiology and brings together laboratory science and child health professionals from multiple disciplines. Her research has covered a broad scope of child health issues ranging from adverse reproductive outcomes, child growth and development, respiratory health, and childhood precursors of adult diseases.

At present, Dr. Wang is the principal investigator of four molecular epidemiological studies on preterm birth, low birth weight, and fetal growth restriction, particularly the interaction between genes and the environment. Her work is supported by grants from the National Institutes of Health and the March of Dimes Birth Defect Foundation.

## Constance Campbell Memorial Research Awards

Six awards were presented at the end of the 2004 Minisymposium. The winners were:



First place poster winner Sharron Hart with NU alumni speaker Dr. Deborah DeManno

### Oral Presentations

**1st Place** - Joanna Burdette, Northwestern University, *Induction of cell cycle arrest by activin A through smad activation in breast cancer cells.*

**2nd Place** - Christina Matulis, Northwestern University, *Identification of the LIM-domain protein FHL2 as a novel coactivator of the orphan nuclear receptor LHR-1 in the ovary.*

**3rd Place** - Bradley Cooke, Northwestern University, *Sex difference in excitatory synaptic input to prepubertal medial amygdala neurons.*

### Poster Presentations

**1st Place** - Sharron Hart, Northwestern University, *ER $\alpha$  immunoreactivity in perisomatic inhibitory synapses and axons in hippocampal CA1.*

**2nd Place** - Melissa Chamberlin, Northwestern University, *Androgens inhibit ATP-sensitive potassium channel subunit mRNA expression in the male rat preoptic area and medial basal hypothalamus.*

**3rd Place** - Jason Hickok, University of Illinois, *Diurnal expression of clock genes in native gonadotropin-releasing hormone neurons.*



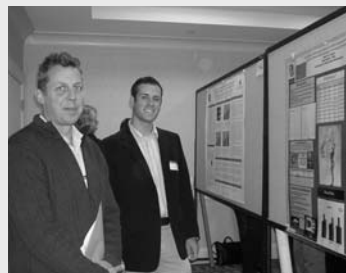
Third place poster winner Jason Hickok



Dr. Jon Levine and keynote speaker Dr. William F. Crowley Jr.



Dr. Janice Bahr and Jorie Aardema



Dr. Andrew Wolfe and Jason Lange



Dr. Fred Turek, NU alumni speaker Dr. John Kirby and Dr. Erv Goldberg

## RESEARCH NOTES

Research Notes features the recent laboratory findings of a CRS member. This issue we focus on the laboratory of **Serdar E. Bulun, M.D.**, a Northwestern faculty member and an internationally recognized physician scientist in the field of estrogen biosynthesis in hormone-dependent human diseases, such as breast cancer, endometriosis and uterine fibroids.

The research of Serdar E. Bulun, M.D. focuses on the field of estrogen production in human diseases such as breast cancer, endometrial cancer, endometriosis and uterine fibroids. All of these common diseases comprise some of the most important public health problems of women in the United States. It is estimated that a total of 30 million U.S. women suffer collectively from one of these estrogen-dependent diseases.

Aromatase is an enzyme that is essential for the production of estrogen. A group of medications called aromatase inhibitors stop the activity of the aromatase enzyme and therefore stop estrogen production in the human body. Aromatase inhibitors are currently the most commonly used and most effective non-toxic medications in the treatments of breast cancer.

There are several major areas of research in Dr. Bulun's laboratory that link aromatase to breast cancer, endometrial cancer, endometriosis, and uterine fibroids. A group of scientists work on the link between aromatase and breast cancer. On average, women have a 1 in 7 risk of being diagnosed with breast cancer sometime in their lives. Breast cancer is the most common and deadly malignancy of women. Work from Dr. Bulun's laboratory has shown that the most important location for estrogen production is the breast cancer tissue itself because large amounts of aromatase are present in breast cancer tissue. Breast cancer tissue is made up of malignant cells and surrounding fibroblasts. Dr. Bulun's work has shown that aromatase is induced by multiple redundant mechanisms in the fibroblast component of breast tumors.

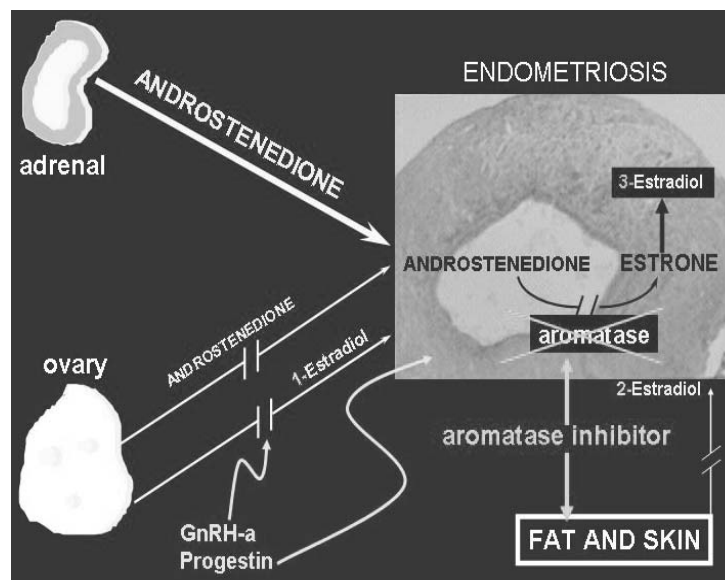
Thus, estrogen made in breast fibroblasts cells causes of the growth of the neighboring malignant cells. The clinical importance of these laboratory findings have been underscored by the common use of aromatase in the treatment of breast cancer.

As in the case of breast cancer, endometrial cancer is also dependent on estrogen for development and growth. Work from this laboratory also shows that various molecular mechanisms contribute to the presence of aromatase and formation of estrogen in endometrial cancer. In fact, early studies have now shown that the targeting of aromatase treats endometrial cancer in the early phase of this disease.

One of the most prominent areas of research in the Bulun laboratory is endometriosis. Endometriosis is an extremely painful disease of women characterized by the presence of the inner lining of the uterus or menstrual tissue on pelvic organs such as ovaries, tubes, bladder, or bowel. It is characterized by severe pain and infertility and affects approximately 5-10 million women in the U.S.

Aromatase is present in endometriosis tissue. Not surprisingly, endometriosis tissue is dependent on aromatase and estrogen for growth. Work from Dr. Bulun's laboratory has shown that estradiol is produced in pre-menopausal women in 3 major sites (*see figure*). First, it is secreted from the ovary into the bloodstream. Only this source of estrogen has been known and addressed in the treatment of endometriosis (*see figure*). Therefore, women were treated with a GnRH agonist (GnRH-a) such as lupron or a progestin to stop stimulation of ovaries by hormones that arrive from the brain. This type of treatment would stop the ovarian estrogen from reaching endometriosis tissue. Unfortunately, only half of the patients benefit from these treatments.

Recent work from Dr. Bulun's laboratory has identified two additional sources of estrogen (estradiol). Fat and skin tissues also contain aromatase and make estrogen (*see figure*). Moreover, estrogen is also made by the presence of aromatase in endometriosis tissue.



The precursor steroid androstenedione arrives at the endometriosis tissue by way of the bloodstream. In the endometriosis tissue, androstenedione is converted to estrogens such as estrone and estradiol by the action of aromatase enzyme. Estradiol is especially biologically active. Estradiol closes the growth of endometriosis tissue. This research led to the introduction of aromatase inhibitors for the treatment of endometriosis. Preliminary pilot trials conducted by different physician scientists in Dr. Bulun's team have been extremely successful, in that women who do not respond to

other medical treatments for endometriosis (such as GnRH agonists or progestins) have responded positively by decreased pain to aromatase inhibitors (*see figure*). Dr. Bulun's team continues to find new targets in these pathways to treat endometriosis.

Finally, the Bulun laboratory works on mutations that are transmitted from parents to children that turn on aromatase inappropriately in many tissues and give rise to excessive estrogen formation. We have identified several families across the world that are affected by this syndrome. These affected patients have gynecomastia (feminine growth of breast tissue in males), decreased testicular function in males, early breast development in girls, and irregular menstrual bleeding and abnormal uterine growth in females.

Dr. Bulun and his laboratory will continue to work on this newly defined genetic syndrome of aromatase excess and find its possible roles in common diseases in women such as breast cancer, endometrial cancer, endometriosis, and uterine fibroids.

## RECENT PUBLICATIONS

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## Training Grant Enters 26th Year at CRS

The Training Program in Reproductive Biology has both a long history and a bright future. The Program, directed by Dr. Jon E. Levine, is entering its 26th year as the first of an additional five years of support that was recently awarded by the National Institute for Child and Human Development. This is the fifth 5-year renewal of the Training Grant, providing support for three postdoctoral and four predoctoral fellows into the 30th year of the program.

The training grant was initially awarded to Dr. Neena B. Schwartz, prior to the formation of the Center for Reproductive Science (CRS). Northwestern's Program for Reproductive Research, the precursor of CRS was started in 1974. Faculty members involved in this program were interested in doing collaborative research and so, under the guidance of Dr. Schwartz applied for a Training Grant from NIH.

The grant was awarded in 1978 and it's first preceptors, in addition to Dr. Schwartz, were Fred Turek, Ph.D., Connie Campbell, Ph.D., Erwin Goldberg, Ph.D., Mary Hunzicker-Dunn, Ph.D., and Gwen Childs, Ph.D.

The training grant was the Program's first multi-investigator grant with preceptors from both Evanston and Chicago campuses with collaboration between clinical and basic science research. The success of the training grant program, as well as the Program Project Grant awarded in the 1980's from NICHD, eventually led to the founding of the Center for Reproductive Science in 1987 with Dr. Schwartz serving as the Director.

The purpose of the training program is to educate predoctoral and postdoctoral fellows in specific areas of reproductive biology, within the framework of an integrated, multidisciplinary program offering a uniquely broad perspective of the reproductive sciences. Specific areas of training are:

1. Reproductive endocrinology - hormonal interactions among the hypothalamus, pituitary, and gonads; molecular and cellular actions of neuro-hormones, gonadotropins, and gonadal hormones, and control of their secretions.
2. Cellular, molecular, and hormonal events controlling folliculogenesis and gametogenesis.
3. Sex determination and reproductive development - molecular genetics of sexual differentiation, organizational effects of gonadal steroids, and mechanisms governing sexual maturation.
4. Pregnancy - molecular endocrinology and cell biology of the placenta.
5. Environmental and metabolic control of reproduction - neural mechanisms that integrate energy balance and reproductive processes, and mediate reproductive effects of environmental variables.

The Directorship of the Training Grant was passed from Dr. Schwartz to Dr. Turek in 1988, and from Turek to Dr. Levine in 1990. After 14 years as Director of the Training Grant, Dr. Levine will pass the Directorship forward to Dr. Teresa Woodruff in 2005. The current roster of preceptors in the Training Program includes: Andrea Dunaif, M.D.; Erwin Goldberg, Ph.D.; Mary Hunzicker-Dunn, Ph.D.; J. Larry Jameson, M.D., Ph.D.; Jon Levine, Ph.D.; Daniel Linzer, Ph.D.; Kelly Mayo, Ph.D.; Fred Turek, Ph.D.; Teresa K. Woodruff, Ph.D. and Catherine Woolley, Ph.D.

### Meet the Trainees:

#### Predoctoral Trainees:



##### Hena Alam

Hena is working on aspects of PI 3 kinase signaling in the Hunzicker-Dunn lab. She earned her B.S. in Biochemistry in 1996 from the University of Chicago.



##### Melissa Chamberlin

Melissa is a third-year graduate student in the Levine lab. She earned her B.S. in Biology from the University of Michigan in 2002. Her research focuses on the molecular basis of androgen action on neuroendocrine systems.



##### Robert Cook

Bob joined the Woodruff lab in June 2001, and is a fourth-year IBiS student. He graduated from Temple University in Philadelphia, Pennsylvania in 1993 with a B.S. in Biology. His work focuses on the structure of inhibin and its antagonism of activin.



##### Christina Matulis

Christina's studies are in the area of transcriptional coactivators for the orphan nuclear receptors SF-1 and LRH-1 in the ovary. She is a graduate student in the Mayo lab and earned her B.S. in Biology from the University of Illinois

#### Postdoctoral Trainees:



##### Joanna Burdette, Ph.D.

Joanna joined the Woodruff lab as a postdoc in August 2003. She earned her Ph.D. from the University of Illinois at Chicago in 2003, working on herbal alternatives to hormone replacement therapy. She is now working on activin's role in mammary carcinogenesis and physiology.



##### Lisa Henry, Ph.D.

Lisa earned her B.S. at Boston College and Ph.D. at State University of New York at Binghamton. She joined the Levine lab in April 2003. Lisa's research focuses on uncovering the metabolic cues that may regulate the onset of puberty and the maintenance of reproductive processes in adulthood. Identifying these signals and understanding their molecular mechanisms of action in the brain may help to uncover the etiology of certain fertility diseases, such as polycystic ovarian syndrome.



##### Xiangrong Kong, M.D., Ph.D.

Xiangrong joined the Linzer lab in 2002. She earned her M.D. and Ph.D. from Suzhou University in China. Her current research interest focuses on two placenta specific hormones, which she and others have found to be involved in early hematopoietic developments. Besides studying functions of these two proteins during pregnancy and in hematopoiesis, she is also interested in understanding how these functions are regulated, which may lead to exploration of the potential pharmaceutical role of these hormones.

## Student Achievements

**Bethany Freedman** (Jameson/Weiss Lab) defended her Ph.D. Her title was "A Dominant Negative PPARgamma Knock-in Mouse exhibits features of the Metabolic Syndrome"

**Beiyan Zhou** (Linzer Lab) completed her Ph.D. in 2004 working on hormones of pregnancy that regulate the hematopoietic system. She is now a postdoctoral fellow with Harvey Lodish at the Whitehead Institute, MIT.

**Hilary Kenny** (Woodruff Lab) received her Ph.D.. She studied the differential secretion of ovarian inhibin A and inhibin B conducting a comprehensive in vivo study. She is headed to University of Chicago to do postdoctoral research with Ernst Lengyel, M.D.

**Magda Suszuko** (Woodruff Lab) received her Ph.D. Her research was on regulation of follicle-stimulating hormone beta-subunit (FSHBeta) by activin. Her project was designed to identify molecular mechanisms that lead to activin-mediated FSHbeta transcription. She will continue her research in the Woodruff lab as a postdoctoral fellow.

**Anjali Malipatil** (Woodruff Lab) was awarded the Marcia L. Storch Scholarship for Undergraduate Women.

## UPCOMING EVENTS

### February 14, 2005

CRS PO1 Seminar: **Carole Mendelson, Ph.D.**, University of Texas Southwestern Medical Center at Dallas

### March 3, 2005

CRS U54 Seminar: **Yoel Sadovsky, M.D.**, Washington University in St. Louis

### April 11, 2005

CRS Training Grant Seminar: **Jurrien Dean, Ph.D.**, National Institute of Health

### May 9, 2005

CRS Seminar: **Shunichi Shimasaki, Ph.D.**, University of California, San Diego

### May 15-June 26, 2005

Frontiers in Reproduction (FIR), Woods Hole, MA

### September 19, 2005

CRS Seminar: **Mary Zelinski-Wooten, Ph.D.**, Oregon National Primate Research Center

### October 17, 2005

**26th Annual Minisymposium on Reproductive Biology**  
**J. David Puett, Ph.D., University of Georgia**

## Faculty Honors

**Dr. Andrea Dunaif** has been named president of the Endocrine Society for 2005-06.

**Dr. J. Larry Jameson** was elected to the American Academy of Arts and Sciences.

**Dr. Kelly Mayo** was named William Deering Professor of Biological Sciences. He has also been elected to the Endocrine Society's governing council.

**Dr. Thomas McDade** was awarded the Presidential Early Career Award for Scientists and Engineers by the White House Office of Science and Technology Policy.

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