

# Hope FOR FERTILITY — in the Face of Cancer

**O**n a recent Thursday, reproductive biologist Teresa Woodruff '89 PhD, just home from a work trip to India, drove to her lab at the Robert H. Lurie Medical Research Center on East Superior in downtown Chicago, reviewed grant proposals with two of the 32 members of her team and then met with a former colleague who works for a health tech nonprofit run by the founder of eBay and his wife. Then Woodruff sat down with a research assistant professor who helps oversee her many studies.

Just before noon, she zipped her MacBook into a purple cover and slung her purple purse over her shoulder. Then she walked to lunch at the Arts Club of Chicago with legal scholar Leigh Buchanan Bienen, wife of former Northwestern president Henry Bienen '09 H.

Next, Woodruff trekked to Central DuPage Hospital in Winfield, Ill., to give a continuing medical education lecture on oncofertility — a word she coined in 2006 to refer to the medical field that she created. Oncofertility helps young cancer patients preserve their ability to become biological parents even after chemotherapy and radiation. The subtitle of her talk was “Bench to Bedside to Babies.” With new breakthroughs, it is possible to “change a devastating diagnosis into life-affirming interventions,” says Woodruff. “The reason we do basic science is to improve the health of tomorrow’s patient. Ultimately, it’s also satisfying to know that the science you do can transform people’s lives.”

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Welcome to the world of Teresa Woodruff. The Thomas J. Watkins Memorial Professor of Obstetrics and Gynecology and former president of the Endocrine Society — who has appeared on *Time*’s list of most influential people and has received the Presidential Award for Excellence in Science, Mathematics and Engineering Mentoring at the White House from President Barack Obama '06 H — directs Northwestern’s Center for Reproductive Science and its Women’s Health Research Institute, which she founded. This fall she is teaching seven students in the inaugural class of her new 18-month master’s program in reproductive science and medicine, professionals who could become embryologists at in vitro fertilization labs, schoolteachers or future medical students.

When she isn’t teaching or doing research, Woodruff advocates for improvement of U.S. health policy. For example, she helped persuade the National Institutes of Health to change its policy so that as of Jan. 25, 2016, females — from animals to people — must be considered in all NIH-funded studies. At a press conference after a September visit to Northwestern’s Chicago campus, NIH director Francis Collins called studying both genders “a critically important issue” and said it has already reduced health care costs “140-fold” by showing what works and what doesn’t work.

Woodruff and Melina Kibbe '03 GME, her friend and former Northwestern colleague, now chair of the surgery department at the University of North Carolina at Chapel Hill, had drawn national attention to the lack of sex equity in research when they highlighted the underrepresentation of female cells and animals in basic science studies in a *60 Minutes* segment.

It all started one day during lunch, when Kibbe shared her promising findings on the use of nitric oxide to treat scar tissue that forms after vascular surgery — and Woodruff asked, “Have you studied the result in females?” Kibbe promptly purchased female rats and reran the study. To her surprise, the female rats needed much higher doses of nitric oxide than male rats. Indeed, adverse effects in women are a leading reason why the U.S. Food and Drug Administration

**THROUGH PIONEERING RESEARCH  
IN ONCOFERTILITY, REPRODUCTIVE  
ENDOCRINOLOGIST TERESA WOODRUFF  
OFFERS YOUNG CANCER SURVIVORS  
OPTIONS TO HAVE CHILDREN.**

**by Karen Springen**

*Teresa Woodruff outside the Woodruff Lab in the Robert H. Lurie Medical Research Center in Chicago. The bulletin board on the left welcomes high school students to the Oncofertility Summer Academy, with photos of each of the participants.*

**FERTILITY PRESERVATION**

Researchers at the Northwestern-based Oncofertility Consortium are exploring several ways to help women and men who face questions about their future fertility after undergoing cancer treatment, including surgery.

Reproductive endocrinologist **Teresa K. Woodruff** established the consortium to expand fertility options for cancer survivors.

**For women,** standard methods include:

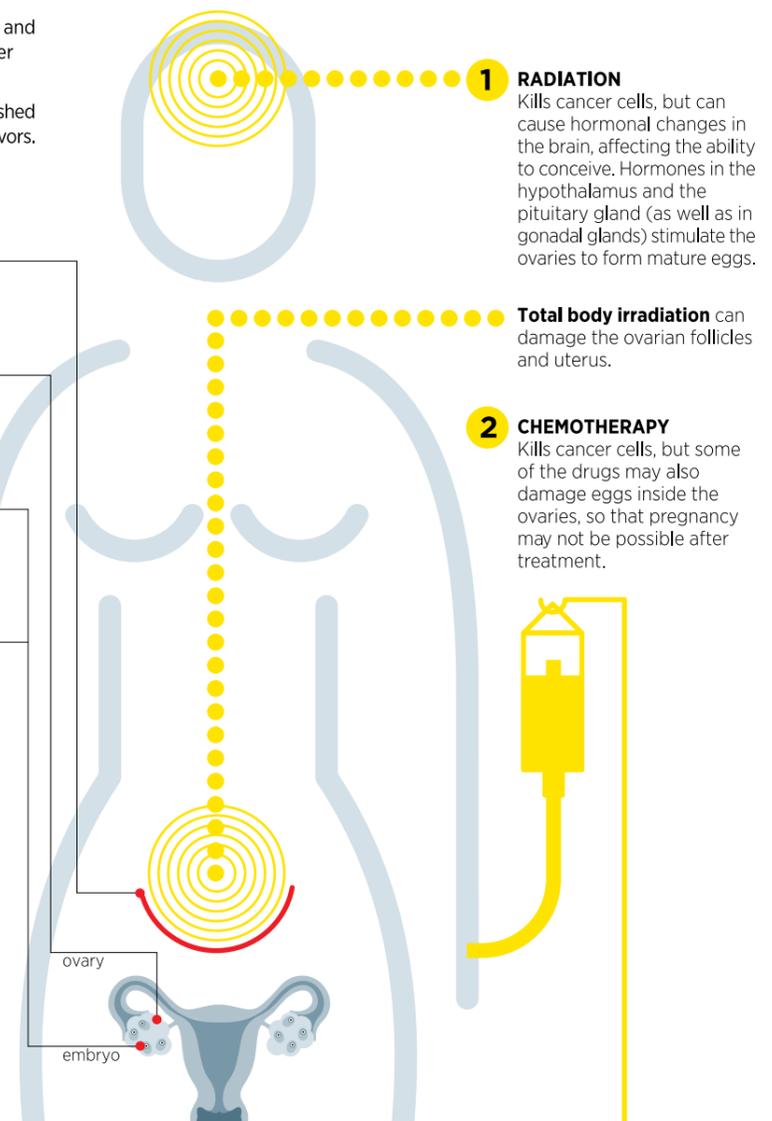
- 1 PELVIC SHIELDING**  
It may be possible to protect one or both ovaries during radiation therapy.
- 2 OVARIAN TRANSPOSITION**  
Before radiation one or both ovaries are moved to the abdomen or pelvis, away from the radiation field.
- 3 EMBRYO BANKING**  
Eggs are surgically removed and frozen or fertilized and then the embryos are frozen.
- 4 UNFERTILIZED EGG BANKING**  
Following fertility drugs to boost production, immature eggs are surgically removed and frozen.

Experimental methods include:

- 5 OVARIAN TISSUE BANKING**  
Small pieces of the ovary are removed and frozen. Transplantation may be possible after cancer therapy.
- 6 IN VITRO MATURATION**  
Immature eggs are surgically removed and matured in a laboratory.

... BEFORE ...

**CANCER TREATMENT**



**1 RADIATION**  
Kills cancer cells, but can cause hormonal changes in the brain, affecting the ability to conceive. Hormones in the hypothalamus and the pituitary gland (as well as in gonadal glands) stimulate the ovaries to form mature eggs.

**Total body irradiation** can damage the ovarian follicles and uterus.

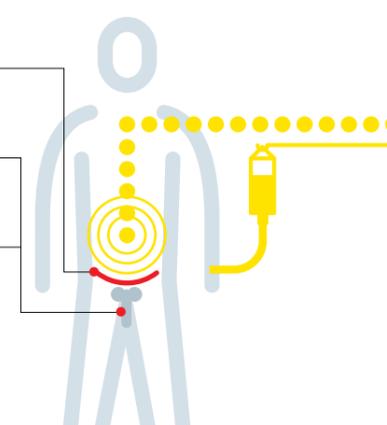
**2 CHEMOTHERAPY**  
Kills cancer cells, but some of the drugs may also damage eggs inside the ovaries, so that pregnancy may not be possible after treatment.

**For men,** the preservation of fertility is less complicated than it is for women.

- 1 TESTIS SHIELDING**  
Protects the testes during radiation therapy.
- 2 SPERM BANKING**  
The patient produces a sample of his sperm, which is frozen.
- 3 SPERM EXTRACTION**  
If the patient is unable to produce a sample, sperm can be surgically obtained, then frozen.

Experimental method:

- 4 TESTICULAR TISSUE FREEZING**  
A small piece of the testis is surgically removed and frozen for possible use in a future treatment.



**RADIATION & CHEMOTHERAPY**  
Kill cancer cells, but the testes are highly susceptible to these therapies (at all ages); can cause long-term damage to sperm cells, and, therefore, to a man's fertility.

removes drugs from the market and why some popular medications, such as the sleeping pill Ambien, now carry different suggested doses for different sexes.

"I never would have gotten involved in advocacy at this level if it weren't for Teresa's inspiration," says Kibbe. "She's a role model for me and just so damn inspiring."



Woodruff is known as a champion for interdisciplinary work and collaboration, within Northwestern and around the world.

"She's been very fearless about seeking out people who do work different from her own," says biochemist Kelly Mayo, associate dean for research at the Weinberg College of Arts and Sciences, who was Woodruff's doctoral adviser at Northwestern and her collaborator for the past three decades. She has reached out to ethicists, bioengineers, oncologists, even app developers.

Woodruff founded and leads the international Oncofertility Consortium, based at Northwestern, an interdisciplinary initiative that includes members in 117 countries and addresses the complex health care and quality-of-life issues that concern young cancer patients whose fertility may be threatened by their disease or its treatment. The consortium also hosts an annual oncofertility conference to discuss science and research and brings together experts in areas such as reproductive medicine, oncology, materials science, bioethics, religion and education to look at mechanisms underlying the fertility threat from cancer drugs and other topics, such as methods for freezing, storing and growing gonadal tissue and ethical and legal concerns regarding the use of fertility preservation technologies in cancer patients.

Among Woodruff's longtime collaborators on human follicle growth is Lonnie Shea, now chair and professor of the department of biomedical engineering at the University of Michigan and an adjunct professor of obstetrics and gynecology at Northwestern. Woodruff knows the biology of the ovary, and he knows how to produce replacement tissues. "There was this natural synergy there," says Shea.

Woodruff also collaborates with Northwestern colleagues in the humanities and social sciences. For example, she is working with Ellen Wartella, communication studies department chair and Sheikh Hamad bin Khalifa Al-Thani Professor of Communication, and *Blue's Clues* animator Eric Patrick, an associate professor in the School of Communication, to create "The New You, That's Who," *Schoolhouse Rock!*-like animated cartoons about puberty, reproductive anatomy and menstruation set to original music. Woodruff introduces each cartoon, dressed in her lab coat with a microscope in hand. They'll be screened at the oncofertility conference in November, and then they'll be posted on a new website next April and launched through schools and physician outreach.

Woodruff is entering the 11th year of her Oncofertility Saturday Academy for high school students, which has expanded to the University of California, San Diego, the University of Oregon and the University of Pennsylvania.

She wants the teens to "understand their own reproductive health." The program brings in a diverse population of high school girls and encourages them to explore basic science and clinical applications and career options in reproductive science, cancer biology and oncofertility.

Two alumni became Northwestern undergraduates, and two have gone to medical school, though not at Northwestern.

With Harlan Wallach '00 MFA, associate director of media and design for Northwestern University's information technology department, she received a five-year NIH grant that has allowed them to create Reppedia.org (a laywomen-friendly glossary that explains terms like amniocentesis and zygote), MyOncofertility.org (her patient-facing site) and the iSaveFertility app. She also created an online class for Coursera called Introduction to Reproduction, which has more than 7,000 learners. "She's a force of nature," Wallach says.



Woodruff, who considers herself first and foremost a reproductive science professor, refers to the "teaching gene" in her family. Her father taught at her undergraduate alma mater, Olivet Nazarene University in Bourbonnais, Ill. And she grew up planning to become an elementary school teacher like her grandmother and her mother, who taught her about volcanoes and earthworms. "Teresa was just into any discovery and

wasn't afraid, like some kids are, to get in the dirt," says her mom, Wanda. Helping her college roommate, a pre-med chemistry major, made Woodruff realize she actually wanted to major in chemistry and zoology. One undergraduate project was working at the California Institute of Technology to study chemical bonds. "What I really wanted to do was understand how the answers in the back of the textbook were derived," she says. "Who were the people asking the questions?"

In 1985 she headed to Northwestern because of the University's strong reproductive science tradition, with professors like Mayo, who had arrived from the Salk Institute, and physiologist and endocrinologist Neena Schwartz '50 MS, '53 PhD, author of *A Lab of My Own*. "[Teresa] was extremely hard working," says Mayo. "She had a penchant for doing gigantic experiments."

"When she was trying to figure out where a gene called inhibin was expressed, she created 110 slides rather than the usual 10 or 12," he says. Small wonder that even as a young scientist back in 1988, she published her results in *Science*, he says.

After finishing her doctorate in just three years, with a remarkable nine published studies, she headed to Genentech Inc. in California for six years. In 1995 Larry Jameson, then chief of the division of endocrinology, metabolism and molecular medicine and later dean at the Feinberg School of Medicine, recruited Woodruff back.

"It might be one of the first examples at Northwestern where basic science departments were interested in formally collaborating with departments in the medical school with someone who really would have a shared role across campuses," says Jameson, now dean of the Perelman School of Medicine at the University of Pennsylvania. She moved her lab to the Evanston campus, and then, when her basic research was "ready for translation," she moved closer to the OB/GYN clinicians on the Chicago campus.

Indeed, Woodruff immediately set to work on what she calls "entrepreneurial science" designed to "solve problems."

"In science, you have to be thinking about what's next," she says. "When you walk to the bench, you have to say, 'I don't know — I'm going to discover — I'm going to test.'" It's not for people who want sure things. "You're always asking the next question," she says. "You have to be comfortable with not knowing the answer at the outset."

**Visit the Woodruff Lab:**  
[www.woodrufflab.org](http://www.woodrufflab.org)

**Visit the Patient Portal:**  
Find fertility preservation resources and materials:  
[oncofertility.northwestern.edu](http://oncofertility.northwestern.edu)

**Visit SaveMyFertility:**  
A resource for adult cancer patients and the parents of children with cancer who want to learn more about preserving their fertility before and during cancer treatment:  
[SaveMyFertility.org](http://SaveMyFertility.org)

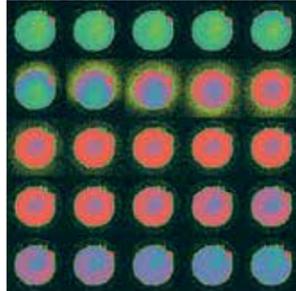
**Call the Fertline:**  
Find a fertility preservation program closest to you  
**Dial 866-708-FERT (3378)**

NIGEL HOLMES

## THE ZINC SPARK

Seven years ago Teresa Woodruff '89 PhD and her husband, chemistry professor Tom O'Halloran, were taking their usual 6 a.m. walk along Lake Michigan near their Rogers Park home. He casually asked her why sperm contains so much zinc. That musing led to a lab experiment with grad student Alison Kim '10 PhD that revealed for the first time that a fertilized egg releases an explosion of zinc at the moment when the sperm makes contact with the egg. "It's a fundamental mechanism no one knew before," says Woodruff. "No one even thought to look!"

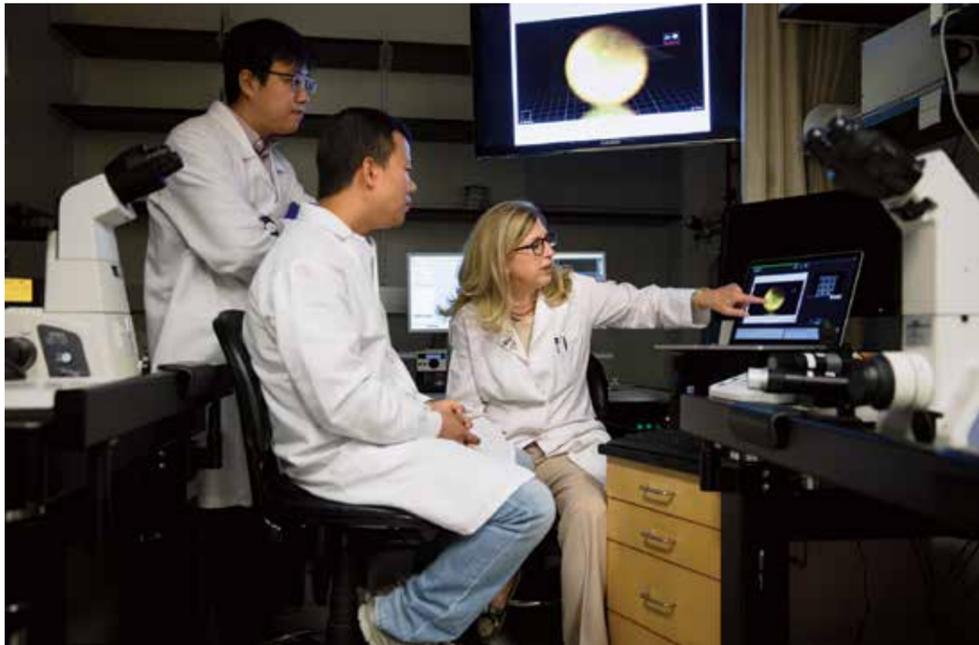
Bigger sparks seem to indicate better quality embryos. So someday doctors might be able to use a noninvasive zinc test to choose the best eggs to transfer during in vitro fertilization. With Francesca Duncan and colleagues and using funds from Ferring Pharmaceuticals (because human egg activation studies are not allowed with federal funds), she and the team have shown zinc sparks occur in humans.



"This is the first experiment that shows that the zinc spark intensity, the amount of zinc released, might correlate with embryo quality," says O'Halloran. "We hope that it will increase the well-being of the offspring from people who go through in vitro fertilization because we think that this might be able to give them the opportunity to only implant a single embryo. The morbidity and mortality in multiple births is significantly greater."

*Discover Magazine* noted the zinc spark as "a major moment in the history of assisted human reproduction" and will highlight the discovery of the zinc spark as one of the top 100 science stories of 2016.

During their 12-year marriage, Woodruff and O'Halloran have maintained another kind of spark — a romantic one — through trips to the Chicago Symphony Orchestra (she grew up playing cello) and to Chicago Cubs games (she is a huge fan). "She knows more about baseball than nine out of 10 guys I know," says O'Halloran. — K.S.



In the Woodruff Lab microscopy suite, Teresa Woodruff and postdoctoral fellows Hoi Chang Lee and Nan Zhang look at images of a mature mouse egg releasing zinc at the time of fertilization.

Currently she is looking for answers to how follicle biology works, how the quality of oocytes (single "germ cells" that can become eggs) can be improved and how the results can be "translated" for patients. Many of her questions started with her wanting to make it possible for all cancer patients, including children who have not reached puberty, to keep the fertility door open. Each year 1.6 million Americans, 10 percent of them in their reproductive years, are diagnosed with cancer. And the survival rate for children has risen to nearly 80 percent.

In fact, today more than 700,000 Americans under age 40 are cancer survivors, according to the American Cancer Society. "You want to know if you keep people alive, what kind of life will they have?" asks Schwartz. Men were already in luck: they could bank sperm. But women weren't always told about preserving their eggs, and doctors didn't think to save ovarian and testicular tissue from young kids. "When I started, most physicians were saying, 'We need to take care of these patients immediately. Don't confuse them with fertility,'" says Woodruff. "Now we have programs around the globe that are addressing this once intractable problem!"

The Oncofertility Consortium National Physicians Cooperative, a group of five dozen or so medical centers under the oncofertility umbrella and also started by Woodruff in 2007, freezes cancer patients' ovarian tissue — 80 percent for the patient and 20 percent for research on so-called "encapsulated in vitro follicle growth," or eIVFG. The goal is to coax the egg in the follicle to grow outside the body, and then fertilize it and put it back in the woman's uterus.

"She is really pushing the boundaries of science and women in science," says Kristin Smith, the patient navigator, who also answers the Oncofertility Consortium's hotline. "We're bringing a message of hope. We're also talking about life after cancer."

Abby Bott, now 29, received that oncofertility message and had her left ovary removed and frozen in liquid nitrogen before getting chemotherapy for stage 3 colon cancer seven years ago. "I was much more thinking, 'Will I live through this?' than, 'Will I be able to have children?'" says Bott. "With cancer in general, the reproductive and sexual side effects are just not talked about. It's seemingly easy for men to preserve their fertility."

Enter Woodruff, whose many entrepreneurial ideas include investigating how to make a pill that would protect the ovaries and keep chemotherapy and radiation from damaging them.

Woodruff also created a 3-D printed bioengineered ovary and a decellularized hormone-producing implant with her former postdoc Monica Laronda '11 PhD, now a tenure-line assistant professor within the fertility and hormone preservation and restoration program at Lurie Children's Hospital, and with materials science and engineering and surgery assistant professor Ramille Capito Shah '00.

"Our goal," Woodruff says, "is to create a durable ovarian bioprosthesis that will provide a cancer survivor with full tissue function — both fertility and hormones — to restore all of the biology lost due to treatment."

"She calls herself a serial collaborator," says Laronda, who considers Woodruff her



Teresa Woodruff in her lab in the Robert H. Lurie Medical Research Center with graduate student Maxwell Edmonds, left, and lab manager Cbris Will behind her

role model. "She is great at understanding what different people need and providing that as a mentor. She has that ability to see everyone's strengths."



Woodruff's mega-lab receives about \$5 million per year in NIH and other funding and employs 18 researchers. "It's really a small business," she says.

She's received extensive NIH support for her EVATAR research, which looks at a bioengineered system that includes fluid flow and tissues connected in a newly invented dynamic environment. The EVATAR includes the major reproductive tissues — ovary, fallopian tube, uterus and cervix — and can be used to measure responses to hormones and reproductive hazards and can be used to screen drugs under development.

"She has a vision, and then she can execute it," says Lauren Ataman-Millhouse '11 MA. Or, as Francesca Duncan, the executive director of the Center for Reproductive Science, says, "The ideas that everyone else has while they're in the shower, she actually [delivers on] those ideas."

Maxwell Edmonds, an MD/PhD student in the Medical Scientist Training Program who would like to make artificial testes for boys with cancer, decided to study with Woodruff after hearing her give a five-minute talk on discovering the biology needed for oocyte health and function and on determining what makes sex cells different from other cells in the body. "She didn't have any slides or handouts, and she was entirely captivating," he says. "Where she thought science was heading was what I thought was fantasy. Teresa really wants to do science that matters for people's health."

Essentially, he says, she was predicting the ability to restore fertility to infertile patients and to learn the basic fundamentals behind the genesis of life before, during and after fertilization. "She said science was heading into an era where advancements on the lab-bench will be quickly translatable to clinical techniques for people's health," he explains, noting that Woodruff and Laronda have restored fertility to infertile mice. "We are, in fact, entering into a time within science that was once reserved solely for science fiction."

The once science-fiction discoveries are now at the forefront of science and medicine. Woodruff's paper on the original discovery that ovarian follicles could be engineered to grow in culture and lead to live healthy offspring (in mice) is listed in the top 1 percent of all engineering articles published in the same time period. And her paper describing the new field of oncofertility in the *New England Journal of Medicine* is in the top 2 percent of all medical articles published in the same time period.

Woodruff remains a medical detective, says Barbara Byrd Keenan, CEO of the Endocrine Society, which is giving Woodruff, a past president, its 2017 award for outstanding leadership.

"Women's system of hormones is probably the most intricate, complex system within the body," Byrd Keenan says. "We're still on the cusp of discovery and finding out how we can intervene with those to either prevent disease, cure disease or promote health." Woodruff is doing all of the above.

"I would tell people to keep an eye on her," says Byrd Keenan.

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