The Grace J. Fippinger Foundation: 7-Year Collaboration Grows Stronger

The Grace J. Fippinger Foundation began a partnership with Women’s Health Research at Yale in 2006 and the bond has grown stronger with critical renewed support over the years.

Our center recently received a fourth grant from the foundation, this time to support our Research Core on Women and Trauma. This interdisciplinary research core studies how experiences of trauma, such as domestic violence or, for military women, exposure to combat, affect physical and mental health in women, and whether gender differences play a role.

“We sincerely appreciate the longstanding commitment of the Grace J. Fippinger Foundation,” said our Director, Dr. Carolyn M. Mazure. “Our partnership has fueled scientific discoveries on how women respond to trauma, and on gender differences in the effects of serious adverse experience. Working together with The Fippinger Foundation, we will make even more progress.”

The Connecticut-based non-profit foundation has enabled our center to advance women’s health on several fronts. Initially, the foundation supported crucial operating costs for research and public outreach. It then aided our development of pilot research that allowed us to receive a U.S. Department of Veterans Affairs grant for a nationwide study on gender differences in female and male military veteran adjustment to civilian life after combat. In addition, the foundation supported our pilot studies in various women’s health areas, including research on cardiac rehabilitation in women, and on obesity, a major health concern with gender differences in its causes and prevention.

Donaghue Foundation Newsletter Celebrates WHRY’s 15th Anniversary - Women’s Health Research at Yale’s success in generating high-impact research findings is featured in the latest edition of The Patrick and Catherine Weldon Donaghue Medical Research Foundation’s newsletter, “Practically Speaking.” The foundation’s crucially important $6.5 million grant in 1998 established what is now Women’s Health Research at Yale.
JOIN THE SOCIETY OF FRIENDS

Consider a donation to Women’s Health Research at Yale in celebration of a birthday, a special occasion, or to honor someone in your life.

Our Society of Friends ensures the future of Women’s Health Research at Yale.

Gifts are welcome at all levels.

To make an online gift visit www.yalewhr.org or mail your gift to Women’s Health Research at Yale

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Women’s Health Research at Yale was founded in 1998 with initial funding from The Patrick and Catherine Weldon Donaghue Medical Research Foundation.
Unexpected Twist: Using an Autoimmune Disease to Fight Cancer

Investigator Rapidly Developing Lupus Discovery into Breast and Ovarian Cancer Treatments

It seems fitting that the autoimmune disease lupus is named for wolves because the ferociousness with which lupus antibodies, proteins designed to protect us, can turn against and attack a patient’s own immune system is astounding.

Yet as harmful as these antibodies can be in lupus, their damaging traits found in one disease are actually being harnessed in the laboratory - in an ongoing Women’s Health Research at Yale-funded pilot study - to develop new treatments for other diseases - breast and ovarian cancer.

Dr. Peter M. Glazer, Professor and Chairman of Therapeutic Radiology, Professor of Genetics and a member of Yale Cancer Center, recently made the astonishing discovery that one type of these lupus antibodies, called 3E10, can kill cancer cells.

It does so by blocking the cancer cell’s DNA-repair mechanism (a mechanism found in every cell to maintain its integrity) and thus shuts the cell down. Lupus patients, unlike those without this disease, create antibodies that penetrate and harm their own cells and DNA (deoxyribonucleic acid), the inherited blueprints for building and operating cells throughout the body. These very cell-penetrating, DNA-targeting capacities are what make 3E10 valuable for cancer treatment.

The tumor-killing power of 3E10, according to Glazer, is even greater when this antibody is combined with cancer chemotherapy drugs such as cisplatin or doxorubicin, or radiation therapy.

Why focus on cancers associated with the BRCA1/2 mutations?

These laboratory findings offer what Glazer considers a direct path to clinical use because many breast and ovarian cancer cells already have a defect in DNA repair, including cancer cells with inherited mutations in BRCA1 and BRCA2 genes. His laboratory work shows that 3E10 antibody used alone or when combined with traditional cancer treatments can have tremendous “killing power” against these cancer cells with BRCA mutations, he said.

These findings gained attention when the discovery by Glazer and his colleagues was announced in October in Science Translational Medicine, an interdisciplinary journal published jointly by the American Association for the Advancement of Science and Science magazine. This publication is at the forefront of reinventing translational medicine to speed the translation of new scientific knowledge into effective health measures.

Glazer received his WHRY Pilot Project Program grant in 2012. It was funded through our collaboration with the Yale Comprehensive Cancer Center to determine, in mice and in cancer cells in the laboratory, which combinations of 3E10 and...
chemotherapy drugs would be most effective at destroying breast cancer and ovarian cancer cells involving the BRCA gene mutations; thus beginning the development of the antibody into cancer therapy.

In the general population, about 12 percent of women (120 out of 1,000) can expect to be diagnosed with breast cancer in their lifetime, compared with about 60 percent of women (600 out of 1,000) who have inherited a BRCA1 or BRCA2 mutation, according to National Cancer Institute estimates. The NCI lifetime estimates for ovarian cancer among women in the general population indicate that 1.4 percent (14 out of 1,000) can expect to be diagnosed with ovarian cancer, compared with 15 to 40 percent (between 150 and 400 out of 1,000) who have inherited BRCA1 or BRCA2 mutations.

Given these increased risks and the fact that breast and ovarian cancers involving BRCA mutations account for sizable populations of women who undergo cancer treatment, Glazer’s discovery and his ongoing pilot research represent fundamentally important developments in dealing with these diseases.

Phase I clinical trials to test the antibody and combinations of the antibody with drugs in volunteer patients are planned within about two years, a fairly expeditious schedule for such human drug trials.

The Science of Discovery

The way Glazer’s serendipitous discovery came about proves the old adage that one person’s poison can be another’s medicine, and demonstrates the value of following research data wherever it leads.

Before the unexpected finding that 3E10 can destroy cancer cells, Glazer and his colleagues had been trying to develop 3E10 as a vehicle for delivering drugs that can protect healthy cells from radiation treatment for cancer or to enhance the effect of radiation against cancer cells. They chose 3E10 as the potential drug-delivery vehicle because it has the capacity to penetrate cells and had been effectively proven safe in humans when tested as a possible lupus vaccine.

Richard H. Weisbart, M.D., a scientist at the University of California at Los Angeles, had isolated the 3E10 antibody from a mouse model of lupus in 1990. The idea then was to create a vaccine that could be given to patients with lupus. UCLA scientists also found that the 3E10 antibody could penetrate cells, making it a good candidate for delivering medication into cells to treat various diseases.

Building on the UCLA findings, scientists at the University Hospital of Lausanne, Switzerland, in 1999 tested the 3E10 antibody as a vaccine in patients with systemic lupus erythematosus, commonly called lupus. The Swiss team found that the antibody was safe, but they dropped development of a vaccine, citing competing priorities.

With the 3E10 antibody cast aside as a possible lupus vaccine, Glazer and his laboratory colleagues set out to use this antibody as their delivery vehicle for enhancing cancer therapy, starting with breast cancer. One of Glazer’s laboratory scientists, James E. Hansen, M.D., Assistant Professor of Therapeutic Radiology, had worked with the UCLA scientists and came to Yale’s residency program after earning his medical degree. While in clinical training in radiation oncology, and as part of his residency he chose to conduct research in Glazer’s laboratory. He was working with Glazer on developing 3E10 as the delivery vehicle for certain proteins, or cell building blocks, that can protect cells from radiation damage during cancer treatment.

“The serendipity came when we tested the effect of the antibody alone on how cells reacted to the radiation,” Glazer said. “Surprisingly, we found that cancer cells treated with the antibody - alone - were more vulnerable to the effects of radiation.”

They stared at the data for quite awhile and
thought something in the laboratory had to have been done incorrectly, or the data itself had to be wrong. “It certainly wasn’t what we were looking for,” Glazer said, recalling that he finally realized the data were correct and told Hansen, “I think you have a new project now.”

As a medical researcher, Glazer said, “you live for these moments.”

And that is where Women’s Health Research at Yale’s support enters the picture, enabling the important laboratory work to move this antibody from discovery toward treatment.

Glazer said it is unlikely that the antibody will cause unexpected toxicity in patients, given the testing in Switzerland. But he will still need to follow a painstaking process to create a therapy that will pass muster in U.S. Food and Drug Administration toxicology testing. And he still needs to find a biotechnology or pharmaceutical firm as a drug-development partner.

Since graduating from Harvard College in 1979, and coming to Yale for a combined M.D./Ph.D. program, Glazer has always kept one foot in medical research and the other in clinical practice. The excitement of discovery and the satisfaction of developing a discovery to improve the lives of his patients make laboratory work meaningful, he said.

“It gives you an extra sense that what you are doing is worthwhile,” Glazer said. “This (3E10 antibody) could be the first thing to come out of my lab that could be given to a patient for treatment.”

**Terminology and Definitions**

**Antibody:** A specialized protein (immunoglobulin) produced by the immune system to counter the introduction of an invading substance. The antibody combines with the invader to destroy it.

**Systemic lupus erythematosus:** Autoimmune disease commonly known as lupus, or SLE. Women account for 90 percent of cases. Instead of producing antibodies to attack invading substances (viruses, bacteria), the immune system in lupus creates autoantibodies that attack the immune system itself.

**3E10:** An autoantibody created by the immune system in lupus. Dr. Glazer discovered that 3E10 can destroy cancer cells, a capacity enhanced when 3E10 is combined with cancer therapies.

**DNA:** DeoxyriboNucleic Acid - the carrier of our inherited genetic material, determining the makeup of all cells. DNA molecule includes two strands of nucleotides linked together in a structure resembling a ladder twisted in a spiral - the double helix.

**BRCA1 and BRCA2:** Human genes belonging to a class known as tumor suppressors. A woman’s risk of developing breast and/or ovarian cancer is greatly increased if she inherits particular BRCA1 or BRCA2 mutations. These inherited mutations also increase risk of breast cancer recurrence. Genetic tests are available to check for these mutations, and genetic counseling is recommended before and after testing.
Almost two years ago, Tomoko Udo, Ph.D., was selected through a national search as one of our four BIRCWH scholars. Our NIH-funded program - Building Interdisciplinary Research Careers in Women’s Health, or BIRCWH - launches the careers of investigators studying women’s health and incorporating gender differences into their studies.

As a Scholar, Udo became part of the faculty in Yale’s Department of Psychiatry and, since the start of her faculty training, has effectively bridged her interest and experience investigating addiction with new studies that examine eating behaviors. Her interest in this emerging field was piqued as she recognized the neurobiological overlap found both in more traditional addictions and eating behaviors leading to obesity. Since coming to Yale, Udo’s new focus has been to better understand the eating behaviors that could, in part, underlie the obesity epidemic.

In a January 2012 report by the U.S. Department of Health and Human Services, national data regarding the prevalence of obesity among children, adolescents, and adults revealed that one-third of all adults and almost 17% of children and adolescents were obese in 2009-2010. The incidence of obesity was higher among older women compared with younger women, while in men there was no age difference in the prevalence of obesity.

If these numbers aren’t staggering, consider the following, published by the Centers for Disease Control and Prevention (CDC) in 2013:

- Obesity-related conditions include heart disease, stroke, type 2 diabetes and certain types of cancer, some of the leading causes of preventable death.
- In 2008, estimated medical costs associated with obesity were $147 billion; the medical costs for people who are obese were $1,429 higher than those of normal weight.
- By 2030, it is predicted that annual health care costs associated with being overweight or obese will exceed $850 billion. (Gearhardt et al, 2011)

The problem is far reaching and of paramount importance, making the potential for findings explaining the reasons for the epidemic to be of great practical benefit to the health of the nation as well as the healthcare system. Drawing on her background in public health, Dr. Udo is committed to translating...
to the clinical setting what she learns in the research laboratory. To achieve this, she consults with clinicians while preparing her laboratory protocols and designs, so that her findings make a strong connection with health practice.

When she began work with her primary mentor, Sherry McKee, Ph.D., Associate Professor of Psychiatry and Director of the Yale Behavioral Pharmacology Laboratory, Udo had an opportunity to work with McKee’s data examining the effects of negative and positive mood induction on eating behaviors. This study, published in October 2012 in the journal *Eating Behaviors*, in which Udo is the first author and McKee the senior author, was the first to experimentally demonstrate that mood state may increase vulnerability to food consumption by reducing the “ability to resist” eating. This ability to resist is the key parameter in McKee’s alcohol and smoking self-administration models - now adapted into a human laboratory model of eating behaviors.

In working with McKee’s data, Udo recognized that the ability to resist palatable food is part of the core issue individuals face in the current food marketplace, where palatable foods are readily available, and a lack of self-control may be strongly linked with obesity. Moreover, this lack of self-control may be more prevalent in women than in men.

In 2011, a group of researchers from the Yale Rudd Center for Food Policy & Obesity and the Department of Psychiatry published an article in the journal *Addiction* entitled, “Can food be addictive? Food health and policy implications,” which describes “hyperpalatable foods” that have invaded the market and changed the way we are exposed to and eat food. These foods are manufactured to surpass the satisfaction derived from traditional foods by increasing certain contents such as fat, sugar, salt, additives and flavors. Although the addictive potential of food is still widely debated, the authors claim that engineered hyperpalatable foods could be capable of triggering an addictive response.

Working on her study design, Dr. Udo incorporated the principles imparted by Dr. McKee’s human laboratory model to test self-control in relation to healthful versus unhealthful food types. In so doing, Udo hopes to elucidate the mechanisms that affect how people eat and make food choices.

Study participants are presented with food choices, six healthful choices and six unhealthful choices. Asked to describe the food, subjects provide subjective opinions about the food items, including the healthfulness of the item and how much they enjoy the taste. The subjects also have the option to eat what they would like but incentives are provided to those who wish to abstain.

Before this laboratory testing, participants complete a self-report questionnaire and cognitive behavioral tasks to determine the level of their self-control tendencies. They are also asked questions about food to gauge their dietary behaviors and knowledge of healthful eating practices.

(Continued on page 8)
Once the food is displayed, Udo takes two important biological measurements:

- the regulation of an appetite hormone, ghrelin; and
- the measurement of heart rate variability.

Heart rate variability allows Udo to track how the person’s autonomic nervous system responds to a food stimulus. A measurement that she had also studied during her time at Rutgers, this variability allows her to note any imbalances, which can be associated with disruptions in behavior - or a less-regulated demeanor. Udo has hypothesized that altered autonomic activity may partially explain unhealthful eating behaviors in obese individuals.

Ghrelin regulation provides a crucial biological measurement, as the level of this hormone increases when a person is hungry, and decreases rapidly once a person begins to eat. Given that altered ghrelin regulation has been reported in obese individuals, and linked to reward-motivated behaviors and cravings, Udo is very interested to see how the ghrelin levels of her study population correlate with their eating behaviors.

This study is currently recruiting subjects, and Udo is looking forward to examining her results.

Through the BIRCWH program, Udo has been able to simultaneously undertake an animal study, working hands-on with her secondary mentor Ralph J. DiLeone, Ph.D., Associate Professor of Psychiatry and of Neurobiology. In this work, she is investigating whether there are gender differences in brain mechanisms of self-control and food intake.

“I’m really thankful for the BIRCWH program in that it has given me the opportunity to pursue multiple models for conducting research. Without having protected time and the freedom to pursue my interests, I would not be able to do this research,” Udo said.

“There is also the element of coaching and mentoring that I’ve been very grateful for. It has helped me better manage my time, which is crucial when you have two ongoing studies,” she said. “It has also provided a sounding board for me to flesh out ideas for papers. Feedback during writing workshops and meetings has been tremendously helpful.”

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### Recent Activities

**Publications**

**Presentations: 2012-13**
- Udo T. Gender/Sex Differences in Self-Control in Addictive Behaviors. Invited talk for colloquium, Department of Psychology. Binghamton University, NY (July 2012).

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### Additional Reading

**Friends & Food**

As this issue of our newsletter features Dr. Tomoko Udo’s work on self-control and eating, we would like to bring your attention to the feature story of the May issue of *New Haven Living – “Friends for a Cause,”* which imparts a story of friendship and food.

Diane Smith, TV journalist, radio host and author, and Mika Brzezinski, author and co-host of MSNBC’s Morning Joe, talk candidly about their honest friendship and struggles with eating and weight. *Obsessed: America’s Food Addiction And My Own,* is available in May.

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Expanding Our Long-Term Commitment to Science that Serves the Public

Women’s Health Research at Yale seeks to reaffirm and expand our commitment to developing research with practical benefits and tailoring medical care by gender to improve individual outcomes for women and men. To attain this future of better health and health care through inventive scientific investigation, we must secure our center’s financial foundation far into the future.

Our long-term success will be ensured only with the partnership and support of leaders who share our strategic view that it is essential to endow Women’s Health Research at Yale’s long-term financial health. Opportunities are available to permanently sponsor a program within our center, with naming recognition of the donor, or sponsor a named study for that study’s duration.

Pressure to generate practically-oriented research findings is increasing, and our progress will be challenged by reduced federal funding for research, decreasing support for training new researchers, and increased demand for rapid translation and communication of findings.

But Women’s Health Research at Yale is well positioned to achieve our goals despite these challenges, because we have built a forward-looking plan, developed key scientific collaborations, and established a stellar record of research success.

Together with strategic partners, our planning will result in expansion of research on women’s health and gender differences, and expeditious conversion of findings into effective clinical care to benefit everyone.

Please contact us at (203)764-6600 for more information on naming opportunities.

Your Donation Can Help Fund New Treatment Developments in Breast and Ovarian Cancer

We are thankful to all of our donors who have helped ensure the success of Women’s Health Research at Yale.

Now, we urgently need your help to secure a matching gift and meet our 2012 Annual Appeal goal. For the second consecutive year, a generous, anonymous donor will match donations dollar for dollar - up to $10,000 - as incentive to help us meet and exceed our target.

This dedicated Friend of our center made this matching gift in honor and admiration of her mother.

Our annual appeal plays a crucial role in funding promising new research like Dr. Peter Glazer’s work (featured in this edition) turning an unexpected laboratory discovery into new therapies for breast and ovarian cancer.

As we approach the close of our fiscal year on June 30th, every gift is important.

With your help, we will cap our 15th-anniversary celebration with unequivocal success by surpassing our goal, and empowering scientists to uncover new ways to improve the health of all the women in our lives.

Thank you!

Patti Russo, Chair
Philanthropy & Communications
Council News...

Two New Members Welcomed

Kimberly Goff-Crews will serve as a Special Advisor to the Council for WHRY. In August 2012, Goff-Crews began her tenure as the Secretary and Vice President for Student Life at Yale University. Goff-Crews had most recently served as Vice President for Campus Life and Dean of Students at the University of Chicago.

A graduate of Yale College and Yale Law School, Goff-Crews first returned to Yale after several years in private law practice, serving as the Assistant Dean in Yale College and Director of the Afro-American Cultural Center from 1992-1998. During this time she worked to enrich the African American student experience at Yale, as well as improve retention rates for women and students of color in the fields of science, technology, engineering, and mathematics.

In particular, when asked by YaleNews about her prior accomplishments, Goff-Crews cited her work with the STARS program - Science, Technology and Research Scholars - which supports minority, women, economically underprivileged and underrepresented students in the sciences.

“I am particularly proud of my involvement in this program...I learned what it meant to be in the sciences and how best to be successful. It was intellectually interesting but also gratifying for me because the program we created, at the direction of faculty, has not only been successful but has transformed lives.”

Women’s Health Research at Yale is very pleased to welcome Bobbi Mark to the Advisory Council. Since graduating as a member of the Yale College Class of 1976, Mark has provided extraordinarily distinguished service to Yale and was awarded the Yale Medal in 2010 - the highest award the Association of Yale Alumni bestows - recognizing her outstanding contributions to the University.

Mark was the first woman in the University’s history to chair the Yale Alumni Fund, and has also served on the Alumni Schools Committee for New York City, the University’s Development Committee, and as a Class Agent, Chair of Regents, Reunion Gift Committee Chair, and Class Council member for the Class of 1976.

She earned an M.B.A. at Stanford University, and was an editor and executive in the publishing industry in New York City, before becoming a professional fundraiser. Mark is now Chief Development Officer for Riverdale Country School, after serving as Vice President for Development at Barnard College and Mount Sinai Medical Center, all in New York City.

Amazing Women in New Haven Living

The May 2013 issue of New Haven Living magazine was all about accomplished women in the state of Connecticut. WHRY Council member Patti Russo, Executive Director of the Women’s Campaign School at Yale, was paid tribute by Anne Worcester, Director of the New Haven Open at Yale and Chief Marketing Officer for Market New Haven. Patti’s mission and passion - to increase the number and influence of women in elected and appointed office in the U.S. and around the world, and to improve quality of life for women through support of research on women’s health, is expressed eloquently.

In the News...

Dr. Carolyn Mazure joins panel at YaleWomen Conference

On April 20th, YaleWomen hosted its inaugural national gathering in Washington, DC, chaired by Ellen Gibson McGinnis,
Class of 1982 and WHRY Advisory Council member. YaleWomen is a global network of Yale women alums committed to advancing women’s voices and perspectives. This conference, themed, “Vision, Values, Voice: Women Changing a Changing World,” looked to inspire and empower participants to make a positive change in their communities and the world.

Dr. Mazure participated as part of the panel of experts for the session “The Two Sex Problem: Gender-specific Health Research.”

**Dr. Harvey Kliman’s Autism Findings**

Those in attendance at the April 4th Women’s Health Seminar Series were given a sneak peek at very exciting research findings by Harvey Kliman, M.D., Ph.D., Research Scientist in Obstetrics, Gynecology, and Reproductive Sciences, and a previously funded investigator through WHRY’s Pilot Project Program.

Dr. Kliman’s results, first reported in an April 25th online issue of Biological Psychiatry, illustrate how abnormalities in the placenta, called trophoblast inclusions, can provide a measure for an infant’s risk of developing autism, providing the opportunity for early diagnosis and treatment for this developmental disorder that effects one out of every 50 children in the United States (CDC).

Currently, most children are diagnosed with an autism spectrum disorder at age 3 or 4, after their first year of life when intervention can be most effective. While Dr. Kliman’s test does not diagnose a child with autism, it can be a tool for parents in providing a better understanding of how their child is developing during the first few years of life.

Dr. Kliman’s findings have been widely covered in national news media.

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**Annual Grand Rounds Presentation:**

**Major Depressive Disorder in Pregnancy, Antidepressant Treatment and their Impact on Birth Outcomes**

On April 5th Kimberly A. Yonkers, M.D. gave the annual Grand Rounds lecture sponsored by the Women’s Behavioral Health Research Division of the Department of Psychiatry.

Dr. Yonkers presented data from the Yale Pink and Blue Study which examined depression and antidepressant use during pregnancy and the risks of depression and antidepressant use on birth outcomes.

While many women discontinued their depression medications during pregnancy, Dr. Yonkers reported, stopping these medications did not lead to an increase in symptoms of depression for most women. For women who continued to take antidepressants while pregnant, the use of selective serotonin reuptake inhibitors was associated with preterm birth (delivery before 37 weeks). Having depression during pregnancy was not related to a greater chance of preterm birth. Neither depression nor taking depression medications were related to a greater chance of early preterm birth (delivery before 34 weeks). Dr. Yonkers stressed the importance of learning more about the relationship of depression and antidepressant medications to pregnancy outcomes in order to best protect both the health of the pregnant woman and the pregnancy.

Dr. Yonkers’ work focuses on the ways that psychiatric disorders like depression relate to the menstrual cycle and pregnancy.

Dr. Yonkers is a Professor of Epidemiology; Psychiatry; and Obstetrics, Gynecology, and Reproductive Sciences at Yale University and the Director of the PMS and Perinatal Psychiatric research Program. She is also a mentor on the Women’s Health Research at Yale’s Yale BIRCWH Scholar program.
Women’s Health Research at Yale
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New Research Video:
“Dietary Protein & Bone Health”

“Nearly fifty percent of women over the age of 50 will have some sort of osteoporosis-related fracture in their lifetime.”

Now available on YouTube & our Video Gallery: www.yalewhr.org

Understand the risk factors associated with osteoporosis by hearing WHRY investigator Dr. Karl Insogna, discuss his work looking at dietary protein and bone health.