Major Gift Endows Named Women’s Health Research Award

Women’s Health Research at Yale jumpstarts highly innovative biomedical and behavioral research with “seed” funding for studies on women’s health never before undertaken. Thanks to an extraordinary $1 million endowment gift from Wendy and Tom Naratil, a Yale College ’83 couple, this critically important work will be greatly expanded.

New annual funding, thanks to this gift, will support investigations that are either highly inventive or close to a major breakthrough in advancing women’s health – where funding is needed to reach their aims.

“The new Wendy U. and Thomas C. Naratil Pioneer Award dramatically increases the reach and productivity of our Pilot Project Program and ensures, in perpetuity, that we can develop vital research in women’s health and gender differences. We thank the Naratils for this very generous, visionary gift,” said Dr. Carolyn M. Mazure, Director of Women’s Health Research at Yale.

The influential findings generated by our pilot studies provide practical benefits to women through improved prevention and development of new therapies for a host of conditions unique or more prevalent in women, as well as produce feasibility data for obtaining external grants that allow investigators to continue the work they have begun.

All Pilot Project Program studies selected for funding must demonstrate new approaches to major challenges in women’s health, and advance knowledge to improve well-being for all.

To learn more, visit our website:
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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

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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.
More than a decade ago, scientists discovered that a greater reactivity to stress in women compared to men was a key reason that women are twice as likely to experience depression, the leading cause of disability worldwide. The neurobiological mechanisms underlying these gender differences in stress effects, however, remained unknown. Dr. Amy Arnsten had wondered whether sex differences in the stress response might influence the pre-fronatal cortex, the brain region that regulates thoughts, actions and emotions, and whether fluctuating levels of the hormone estrogen played a role.

Until she was awarded a Women’s Health Research at Yale Pilot Project Program grant, however, she did not have the dedicated resources to compare stress effects in female vs. male animal models. Using female animals in her laboratory was simply too expensive because female hormonal cycles add complexity and variability – making data more difficult to gather and interpret. After receiving her pilot funding in 2000, she soon demonstrated that the effects of stress on the pre-frontal cortex are more pronounced in females, and that the greater sensitivity in females appears related to higher cyclical estrogen levels.

“I couldn’t have done this without the WHRY grant. It was a great opportunity to be able to study the effects of stress on the pre-frontal cortex in females. Because I was able to use female animal models, the study was also the most clinically relevant for understanding these effects in women,” Arnsten, Professor of Neurobiology and Psychology, said in a recent interview.

Her pivotal findings provided a biological basis for why women compared to men are so much more reactive to stress-related depression and Post-Traumatic Stress Disorder (PTSD). Moreover, the insights gained helped pave the way for further study of the relationship between stress and mood disorders, and supported the effort of a group of Yale scientists to establish a federally-funded research consortium focused on stress. Ultimately the work generated through the consortium enabled prediction of what happens in the prefrontal cortex of people confronted with uncontrollable stress. Most importantly, these neurobiological insights continue to aid development of medications being used to treat a variety of conditions, including depression, PTSD, anxiety disorder, tobacco dependence and other addictions – all of which exhibit gender differences and are particular health concerns for women.

Health Benefits Flow from Findings

Arnsten’s study is one of many Women’s Health Research at Yale Pilot Project Program investigations that have been game changers, whether the influence was immediate (a rare occurrence in science) or represented a key step (the more typical science scenario) on the path to improving health or health care. The findings generated from these “seed” grants have advanced our key missions in a number of other ways:

- Allowing investigators to obtain larger, external grants to further their work on key women’s health conditions
- Launching women’s health research careers, and helping these scientists begin to become seasoned investigators who mentor junior investigators

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Innovations in Women’s Health

Current Research

- Facilitating collaborations and teamwork among investigators to explore emerging, complex questions in a variety of women’s health areas

“Above all, these pilot findings are either directly revealing or pointing to opportunities for providing clinical health benefits, in preventing, diagnosing and treating crucially important conditions that are unique or more prevalent in women, or have gender differences,” said Dr. Carolyn Mazure, Director of Women’s Health Research at Yale.

Dr. Sherry McKee’s work on smoking cessation is another prime example. Smoking is the single greatest cause of preventable illness and death in the United States and one of the leading causes of death globally. Quitting provides tremendous benefits – improved health and longevity, reduced cancer and heart disease risks, and financial savings. Yet breaking tobacco dependency is more difficult for women compared to men.

McKee’s pilot study, funded in 2001, began to explain some of the key behavioral and psychological reasons for this difference. She investigated the relationship between negative mood and smoking behavior, and found that negative mood reduces the time a smoker can resist the next cigarette, and increased the intensity of the smoking. This relationship between negative mood and smoking, McKee found, is stronger in women than men.

“So this started a whole line of research to understand what causes the gender differences in smoking behavior,” said McKee, Associate Professor of Psychiatry. “Very simply stated, our research has demonstrated that smoking to regulate and alleviate negative mood and stress underlies the smoking behavior of women more so than men, whereas men tend to smoke more for nicotine-based reinforcement.” FDA-approved smoking cessation aids are designed to reduce this craving for nicotine, McKee notes, helping to explain why such therapies can be more effective in men, and women have poorer cessation rates.

Research Center to Help Women Quit Smoking

Building on her WHRY-sponsored research, her subsequent work led McKee and her colleagues to apply for and receive a $6.2 million grant in 2012 from the National Institutes of Health Office on Research on Women’s Health and the National Institute of Drug Abuse. This established the Yale Translational Center to Develop Gender-Sensitive Treatment for Tobacco Dependence. Already the center has begun investigating new neurobiological medication targets and behavioral therapies. “We think the targets we are studying are going to be effective for both men and women, but they are going to operate through different mechanisms,” McKee said.

McKee is Director of the new center, Mazure is Scientific Director, and Women’s Health Research at Yale is a close collaborator. Arnsten serves on the new center’s executive committee, and some of the medications integral to Arnsten’s work on mitigating the effects of stress to treat mental disorders are now being investigated as smoking cessation therapies. Typical of so many of the WHRY-funded pilot projects, the results of McKee’s study began a steady stream of clinically-relevant discoveries that continue to elucidate how best to help women and men quit smoking.

Revolutionary New Breast Cancer Model

In addition to smoking cessation and mood disorders, our pilot studies have explored numerous women’s health areas including various types of cancer that are particular concerns for women. These include breast cancer, which strikes 1 in every 8 American women and is the second leading cause of cancer mortality in women in the United States.

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Although breast cancer therapies have improved in recent decades, most drugs developed to treat breast cancer fail because the animal models for testing them do not account for the important role the human immune system plays with tumor pathology and therapy, according to Dr. Joann Sweasy.

Sweasy, Professor of Therapeutic Radiology and Genetics, used a 2009 WHRY pilot grant to develop a mouse model of breast cancer that incorporates the human immune system, allowing her to test the effectiveness of radiation and various chemotherapy drugs in scenarios that more closely resemble patients’ experiences than existing models allow. Her laboratory findings showed that, when radiation therapy interacted with the human immune system, the inhibition of tumor growth was enhanced. She used her results to persuade breast surgeons (with informed consent from patients) to provide human breast tumor fragments, so that the new model now incorporates a patient’s tumor as well as immune system (by putting white blood cells from the patient into the model to produce human immune system cells and antibodies.)

Sweasy ultimately used her pilot study results to help obtain two larger grants for research to perfect the model and lay the groundwork for optimizing the selection of treatments that will be most appropriate for an individual patient’s tumors and immune system – personalized medicine for breast cancer.

“She finds were seeds to grow more studies,” said Dr. Alfred Bothwell, who has worked for years with “humanized” mouse models to study various diseases, and recently began collaborating with Sweasy on maximizing the value of her breakthrough breast cancer model. “My heart is with this breast cancer project,” he said.

Sweasy and Bothwell, Professor of Immunobiology, are now working to identify genetic mutations in a type of breast cancer that is among the most difficult to treat and often recurs after initial treatment – so-called triple-negative breast cancer.

“When we know the genetics, we may be able to enhance the effect of the patient’s immune system in combination with the most effective therapy,” Sweasy said.

“Without those early pilot results, we could not have obtained these further grants to perfect the model with the human immune system, and increase its practical value for treating breast cancer,” she said.

Pilot Grants Launch Research Careers

Dr. Harriet Kluger says she will always remember that her first research funding at Yale was a Women’s Health Research at Yale pilot grant. Her career-igniting project, in 2002, was designed to respond to a critically important need involving breast cancer. Her challenge was to develop a fast, economical way to determine which cancer cells are likely to spread to the lymph nodes or other organs, or recur, after the initial tumor has been removed.

Using the latest automated methods that allowed rapid analysis of hundreds of tumor samples, she identified cellular proteins (cell building blocks) and genes (forms of DNA, deoxyribonucleic acid, that carry instructions for making proteins) that serve as “biomarkers.” These markers allow clinicians to predict which patients need additional therapy and which patients can do without it.

Her pilot data helped Kluger obtain a Susan G. Komen Breast Cancer Foundation grant for further research. She was able to use the analytical techniques developed in the pilot study to identify markers for predicting whether a tumor would respond to a particular therapy. Kluger and her colleagues were also able to refine and simplify their analyses, screening for fewer protein and genetic variables but still obtaining the desired results.

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Breast Cancer Findings
Plant Seeds for Melanoma Research

Kluger, Associate Professor of Medicine (Medical Oncology), fondly recalls being mentored as a WHRY-funded investigator by Dr. David Rimm, Professor of Pathology. “I just got my first mid-career award to enable me to mentor junior faculty in a similar fashion,” she said.

Still seeking biomarkers to guide clinical decision-making, Kluger now is focusing on melanoma – a serious type of skin cancer that is fast becoming a crucial health concern for young women. Though the lifetime risk of melanoma is higher for men than women, the risk is increasing among female adolescents and young adults, Kluger said. The incidence of melanoma has increased rapidly among young women in recent decades, partly because of indoor tanning use, said Kluger, who is both a researcher and clinician at the Melanoma Program at Yale Cancer Center.

Her current research involves identifying genetic mutations as predictive markers in melanoma cells. Using the automated biomarker and genetic analysis techniques she perfected in her breast cancer research, Kluger is now part of a nationally renowned Yale team of surgeons, pathologists, oncologists and a molecular biologist who are translating melanoma research into medications and immune therapy to treat this deadliest form of skin cancer.

Dream Team Develops Microscopic “Smart Bombs” to Kill Cancer Cells

The team science approach to solving the most pressing challenges in women’s health is becoming integral to our Center’s work. A 2010 pilot grant, for example, spurred the formation of a “dream team” of scientists – Drs. Alessandro Santin and W. Mark Saltzman – to develop a radically different way to treat ovarian cancer, the most lethal gynecological cancer. Most women with the disease respond fully to traditional surgery and chemotherapy, but later develop chemotherapy-resistant cancer. Thus, the development of effective treatments for resistant ovarian cancer is a high priority in medicine.

This team combined their special knowledge – Santin as a clinical oncologist and cancer researcher with an understanding of the genetics and vulnerabilities of ovarian tumors, and Saltzman as a biomedical engineer experienced in creating highly-inventive vehicles for delivering drugs to their intended targets – to develop specially designed nanoparticles as microscopic “smart bombs” to latch onto ovarian cancer cells and unleash potent toxins to kill only the tumors.

Santin, Professor of Obstetrics, Gynecology, and Reproductive Sciences, had discovered that genes for making two particular proteins were highly expressed in chemotherapy-resistant ovarian cancer cells. (Gene expression is the process by which information from a gene is used to make proteins, the building blocks of cells.) These two proteins coincidentally are receptors in the surface lining of the ovaries for a potent bacterial poison found in nature, Clostridium perfringens enterotoxin, or CPE. Thus, CPE is an effective substance for both targeting and destroying ovarian cancer cells. Unfortunately, intravenous delivery of CPE is toxic.

So Santin figured that a non-toxic CPE peptide, or protein fragment, with an affinity for sticking to the receptors could be used as a safe targeting agent to find and lock onto ovarian cancer cells. But how could they be delivered solely to the cancer cells? This

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is where Saltzman, Goizueta Foundation Professor of Biomedical Engineering, Chemical and Environmental Engineering and Physiology, and Yale’s first Chair of Biomedical Engineering, entered the picture. He designed and developed biodegradable nanoparticles coated with the CPE peptide to home in on the ovarian cancer cells, and deliver a potent chemotherapy as cargo inside the nanoparticle. The binding activity of the peptide can breach the otherwise drug-resistant tumor cells, and the cargo can be unleashed only when the nanoparticle hits the target, avoiding the destruction of healthy cells – a common problem in cancer treatment.

Using a fluorescent dye on the nanoparticles as a tracer, and utilizing female mice to ensure their results were as clinically relevant as possible, Santin and Saltzman demonstrated that their specially designed nanoparticles can kill resistant ovarian cancer cells. They then used these findings from their WHRY-funded study to obtain a National Institutes of Health (NIH) grant of more than $1.3 million for a larger, five-year project to take the next steps toward translating their new approach into a treatment for ovarian cancer patients.

While continuing to move toward clinical trials with the specially designed nanoparticles, Santin and his team believe they may have pinpointed the source of the drug-resistance in most recurrent, treatment-resistant ovarian tumors, namely, these are cancer cells with stem cell characteristics – including the ability to regenerate after initial treatment destroys most of the cancer. Here again, the same genetic traits that Santin discovered – overexpression of the genes for making two particular proteins – make these cancer cells excellent targets for the peptide-coated, CPE-laden nanoparticles developed in our pilot study.

**More New Ways to Treat Cancer Using Nanoparticles**

Importantly, Santin now sees the opportunity for an immediate clinical benefit of these “homing” nanoparticles. He intends to use the same fluorescence that helped demonstrate success in locking onto the targets in the pilot study to “light up” the resistant tumors so they can be surgically removed – thus minimizing the chance for recurrence. He still needs some sophisticated camera equipment before he can determine if this will work in animal models. But Santin considers this approach very promising, with potential applications in treating endometrial as well as ovarian cancer.

“We can take advantage of the fluorescent dye to visualize the disease,” Santin said. “This may allow us, in real time while performing surgery, to see and remove the resistant tumors. We’re in the process of starting this work.”

Santin also has applied for an NIH grant to load the “homing” nanoparticles with iron oxide, instead of fluorescent dye, as another method to visualize and destroy the target cancer cells, as iron is a material that provides excellent contrast in Magnetic Resonance Imaging, or MRI. Once inside the tumor cells, the iron-oxide-laden nanoparticles would be induced to move with the use of magnets – thus moving and increasing the temperature of the cancer cells. Sufficient heat kills them, without harming healthy cells. “We’re already doing this in animal models,” Santin said.

Ultimately, he said, the WHRY pilot grant that teamed Santin and Saltzman for the first time allowed them to come up with whole new ways of targeting and destroying tumor cells, and prompted the formation of a larger team of oncology clinicians/scientists and nanoparticle scientists for further collaborations to develop effective treatments for a variety of cancers.
Press Notes...

Glimmers of Hope On Obesity Front

The tide may finally be turning in the nation’s obesity epidemic.

After three decades of increasing rates of obesity, rates in young children showed modest declines in 18 states, and adult obesity rates leveled off in almost every state, two studies released in August show.

Although youth obesity rates remain high, the U.S. Centers for Disease Control and Prevention reported on August 9th that there were modest declines among low-income preschoolers in 18 states and the U.S. Virgin Islands, between 2008 and 2011. The improvements, the study said, likely resulted from governmental and parental efforts toward healthier foods and exercise programs in schools and communities.

In addition, adult obesity rates remained constant during the past year in all states except Arkansas, according to an annual study published August 15th by the Robert Wood Johnson Foundation and the Trust for America’s Health. The findings may signal prevention efforts are starting to yield results.

Importantly for women, obesity rates are now essentially the same between genders, compared to a decade ago when the rate was significantly higher for women.

As media reports on these studies indicate, while there is cause for hope, the challenge remains daunting. Progress is minimal and uneven. And the epidemic remains a particular concern for women, as they suffer greater obesity-related health problems than men. Nevertheless, as these studies appear to demonstrate, keeping our attention riveted to this problem can pay off in the end.

Investigator News...

McKee Elected to Research Society on Alcoholism Board

Dr. Sherry McKee, Associate Professor of Psychiatry and a WHRY-funded investigator, has been elected to the Research Society on Alcoholism (RSA) Board of Directors. RSA promotes leading research toward prevention and treatment of alcoholism and provides a forum for sharing information among alcoholism researchers.

McKee’s research focuses on improving treatment for those with nicotine (featured in a special article that begins on page 3) and alcohol use disorders. She is Director of the Yale Translational Center to Develop Gender-Sensitive Treatment for Tobacco Dependence, as well as Director of the Yale Behavioral Pharmacology Laboratory, and the Yale Forensic Drug Diversion Clinic. She has received awards for her research contributions from the Society of Research on Nicotine and Tobacco, the National Institute on Drug Abuse, the American Psychological Association, and RSA.
Insuring a Legacy of Change That Helps Us All

Before I impart my words of encouragement, I want to thank Wendy and Tom Naratil for their remarkable gift to endow annual funding for pioneering women’s health research. News of their exceptional generosity (our cover article) provides the perfect springboard to emphasize the need to ensure Women’s Health Research at Yale’s influential work continues forever.

Federal funding for health research – never mind research on women’s health and gender differences – is being squeezed. So we must take hold of our own future – to assure that we keep growing and flourishing as the leading Center for scientific investigations that result in practical improvements in the well-being of women. A great way to guarantee this for our daughters and granddaughters is through Planned Giving.

There are various ways to accomplish this. One option is a Charitable Remainder Trust. It works like this: As the donor, you transfer cash or assets to the trust (1). The trust pays a percentage of the value of the principal over your lifetime or a term of years to you or beneficiaries you name (2). When the trust terminates, the continuing interest from the principal supports the work of Women’s Health Research at Yale.

Go WHRY!

Now is the time to think big, step up and insure our Center’s plans for dramatic, long-term growth. We need your sustained commitments spanning a number of years to make these plans a reality.

Thank you!

Legacy Society Established

Expanding opportunities for support of Women’s Health Research at Yale, we have established a Legacy Society of those wishing to create testamentary trusts, living trusts or other instruments to benefit our Center’s long-term financial health.

“Thanks to a generous testamentary trust from Rosemary Hudson, one of our original benefactors, we now have another means for people to support us,” said WHRY Director Dr. Carolyn Mazure.

Hudson is the Founder of this new Women’s Health Research at Yale Legacy Society. “To be mentioned as its founder is a huge honor,” she said of this new initiative.

Through the Legacy Society, we hope to encourage gifts that will provide lasting support for Women’s Health Research at Yale’s mission to improve the health of women through scientific investigation.
October is Breast Cancer Awareness Month

Our new “Your Health” page provides information on how WHRY-funded research is advancing detection and treatment of breast cancer!

Go to “Your Health” in the Community section of our homepage for all the details.

www.yalewhr.org

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