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Women’s Health Research at Yale generates research findings that transform the scientific community’s understanding of women’s health, answer important questions, and advance knowledge to improve well-being for all.

To learn more please visit our website at:
➢ www.yalewhr.org

or email us at:
➢ WHResearch@yale.edu

Fippinger Foundation’s Continuing Support Makes a Difference in New Obesity Study

Women’s Health Research at Yale has received a third grant from The Grace J. Fippinger Foundation, as part of our enduring partnership that began six years ago.

The new grant is to support our research on obesity, a major health concern for all that likely has important gender differences in its causes and prevention. Part of this important grant is helping to fund our ongoing study on the particular way that diet-induced obesity begins in women, which will be featured in an upcoming newsletter article.

The foundation, a Connecticut-based non-profit organization, began its partnership with our center through a grant in 2006 that our Director, Dr. Carolyn M. Mazure, identified as crucial operating support for research and public outreach.

In 2009, the foundation gave a second grant to support a pilot study on whether there are gender differences in how female and male military combat veterans readjust to civilian life. This study was able to generate the necessary feasibility data to obtain a $2.2 million grant from the U.S. Department of Veterans Affairs for a collaborative nationwide study of this timely question, as unprecedented numbers of military women returned from Iraq and Afghanistan after combat exposure.

Success in Annual Appeal = Critical New Research

We are faring well in our 2011 Annual Appeal, but there is still plenty of room for giving to reach our most ambitious fundraising goal yet.

With federal health research funding almost certainly to be cut, a gift to Women’s Health Research at Yale now represents a tremendous opportunity for new or already acquainted friends to play a role in research that will advance the development of gender-specific medicine. More than ever, your support is crucial to ensuring our role as the nation’s foremost center for generating new research findings to improve women’s health and sharing them with women across the country. (See Advancing WHRY on page 9.)
JOIN THE SOCIETY OF FRIENDS
Consider a donation to Women’s Health Research at Yale in celebration of the birth of a child, a birthday, or to honor that special 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
P.O. Box 208091
New Haven, CT 06520-8091

Educational and outreach activities are made possible through the generous support of:

The Community Foundation for Greater New Haven
The Grace J. Fippinger Foundation
Maximilian E. & Marion O. Hoffman Foundation, Inc.
Seymour L. Lustman Memorial Fund
Anonymous Donors

Women’s Health Research at Yale was founded in 1998 with initial funding from The Patrick and Catherine Weldon Donaghue Medical Research Foundation.
Finding A Way to “Switch” Off the Spread of Breast Cancer

The National Cancer Institute recommends that women age 40 and older have a mammogram every one to two years as routine early detection for breast cancer. This is because the best way to prevent the growth and spread of cancer is to find the disease as early as possible and remove or destroy the cancerous cells.

Once breast cancer has spread, treatments can delay progression of the disease and prolong survival times but it is not a curable condition. Complications involving the spread, or metastasis, of a primary tumor remain the greatest cause of mortality from breast cancer.

For this reason, researchers have been trying to determine exactly how breast cancer cells invade surrounding tissues and spread. If these processes are understood, the researchers can develop interventions to prevent or limit breast cancer from spreading.

Until a few years ago, Dr. Anthony J. Koleske, Yale School of Medicine Professor of Molecular Biophysics and Biochemistry, was not involved in breast cancer research. He and his laboratory colleagues had been studying how cells change shape and move to spread into surrounding tissue – in the healing of wounds. He had identified particular proteins – essential building blocks of cells – which play critical roles in what he calls this “shape-shifting” process of cell movement.

As he reviewed the literature on these proteins, Koleske became aware that one of the proteins he had identified appeared to be a lynchpin in the formation of protrusions from cancer cells. These protrusions enable cancer cells to degrade and penetrate their outer membranes from within, to begin the invasion of surrounding tissue. Called invadopodia, these protrusions play a key part in the metastasis of breast cancer, which after lung cancer causes the greatest cancer mortality in women.

“We decided to move from studying cell movement in wound healing to these invadopodia,” Koleske said in a recent interview, “because they engage even more pressing health concerns.”

His further research showed that three particular proteins come together to form a control “switch” in breast cancer cells which enables them to poke their way through a membrane and invade surrounding tissues, where they can develop secondary tumors, in blood vessels and other tissues such as the lungs – a common site for the spread of breast cancer.

Dr. Koleske teamed with Dr. Titus J. Boggon, Associate Professor of Pharmacology, and as Co-Principal Investigators the two scientists were awarded a 2011 Pilot Project Program grant from Women’s Health Research at Yale to study this switch and how to keep it from forming. By determining how to disrupt the assembly of these three proteins, they will take important first steps toward developing a new class of drugs that could target this switch and thus limit the spread of breast cancer cells. Currently, there are no drugs that selectively target breast cancer invasion or metastasis.

“We’re delighted that this work has come together...”
and we’re excited by this study,” Koleske said. “We have a long way to go, involving a lot of work and time, yet we are cautiously optimistic that this might turn out to be a critical approach to reducing or preventing metastasis.”

**Interlocking Legos**

To envision the control switch, Koleske suggests picturing the three proteins as interlocking Lego building blocks. In previous laboratory work, Koleske determined that knocking out one or more of these blocks in aggressive human breast cancer cells hampers the cells’ invasive capacity and disrupts their ability to metastasize to the lung in an animal model. “We’ve done enough research to establish proof of principle to know we can make an invasive cell into a non-invasive cell by inhibiting the switch,” Koleske said.

In this new pilot study, co-funded by Women’s Health Research at Yale and Yale Cancer Center, the goal is to identify small-molecule compounds that can disrupt the assembly of the breast cancer invasion switch in living organisms. Many approved drugs are small molecule compounds, characterized by low molecular weight and small size, and a high affinity for binding to proteins and altering their function – traits that are expected to be crucial in disrupting the switch.

**Searching for compounds that will work**

To find candidates for drug development, the team will use the Yale Small Molecule Discovery Core Facility, on Yale’s West Campus straddling West Haven and Orange, to screen thousands of these compounds to identify those with the most potential. Under the direction of Dr. Janie Merkel, Director of Biology, this facility has an inventory of more than 140,000 compounds, both natural and man-made, with varying traits, and employs the latest instruments for rapid screening of hundreds of these compounds at once.

Although there is no guarantee that this study will identify a drug, chances are good that some compounds that work will be found, and can be improved, Koleske said. This is where Dr. Boggon’s laboratory comes into play. “Our lab will test how the compounds interact with the proteins,” Koleske said. “His lab will figure out how to make the compounds work better.”

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**Terminology & Definitions**

**Breast Cancer Metastasis:** Spread of cancerous cells from breast tissue to nearby lymph nodes or other parts of the body. Complications from the spread of a primary tumor are the greatest cause of mortality from breast cancer.

**Proteins:** Building blocks, or fundamental components, of all living cells. Three proteins are believed to come together to form a control “switch” – identified by Dr. Anthony Koleske – that turns on the invasiveness of breast cancer cells.

**Invadopodia:** Protrusions in cell membranes that, in breast cancer cells, are enabled by the control “switch” to begin the invasion of surrounding tissue. The invasion and spread of these cells leads to the formation of secondary tumors, and if unchecked, can lead to metastasis.

**X-Ray Crystallography:** Method of visualizing the arrangement and structure of atoms within a crystal – in which x-rays pass through the crystal and bend, or diffract, in different directions. A three-dimensional picture can be produced from the diffraction pattern.

**Structure-guided Drug Design:** Method for designing drugs based on detailed knowledge of the three-dimensional structure and the functions of cell components or proteins that are the intended targets.
This work takes place literally under a microscope - at the molecular level of the proteins and candidate compounds. One of Boggon’s areas of expertise is turning the proteins into crystal form, so that their structures can be visualized using a technique known as x-ray crystallography. In this process, x-ray beams pass through and bounce off atoms in the crystals, causing the light to bend, or diffract, in different directions. The diffraction pattern is used to discern the three-dimensional details of the molecules under study.

“This will allow us to see the precise structure of the proteins and how the surfaces lock together,” Boggon said. “When we can see – in very high resolution – how the machinery works, we can improve the thing that will jam the machinery.”

One of Boggon’s main aims will be to identify the exact sites where the inhibiting compounds stick to the proteins involved in the breast cancer invasion switch, knowledge which will be critical in improving their disruptive capacity. Once this capacity is optimized, Koleske and Boggon will then test the efficacy of the compounds in disrupting breast cancer invasion using cell cultures in the laboratory.

The two scientists ultimately will use the results of their pilot study to apply for a larger grant from the National Institutes of Health to continue their work on developing a therapy to block the spread of breast cancer cells.

Their longer-term goal is to design a drug based on what they discover from understanding the structures and assembly of the proteins that form the breast cancer invasion switch, and the structures and functions of the inhibiting compounds that they identify and optimize.

They envision in the not too distant future conducting clinical trials with a drug developed through this structure-guided design. The drug would be for use as follow-up therapy after a primary breast cancer tumor is treated with surgery, chemotherapy and radiation.

About the Investigators

Anthony J. Koleske, Ph.D., is Professor of Molecular Biophysics and Biochemistry and Professor of Neurobiology. He received his B.S. from the University of Wisconsin and his Ph.D. from the Massachusetts Institute of Technology. His areas of research interest include understanding how nerve cells develop and deteriorate, cell migration, cancer and metastasis.

Titus J. Boggon, Ph.D., is Associate Professor of Pharmacology. He received both his B.S. and his Ph.D. from the University of Manchester, U.K. His research interests include understanding mechanisms that cells use to send and receive signals using interconnected molecules, and applying such information to drug discovery.
Current Research

BIRCWH Scholar Works In and With Community To Improve Health of Mothers and Their Children

Smoking during pregnancy can harm both mother and child. Prenatal smoking, according to the Centers for Disease Control and Prevention (CDC), is one of the most preventable causes of sickness in infants – associated with 30 percent of low birth weight deliveries and 10 percent of premature births.

Being exposed to smoking while in the womb appears to set the stage for children to have a number of behavioral problems such as attention deficit hyperactivity disorder, or ADHD. But exactly what happens – in terms of developmental effects – to preschool and school age children of mothers who smoked during pregnancy remains largely unknown.

Dr. Megan V. Smith is determined to find out. Smith was selected – from a highly competitive national field – to fill one of four junior faculty research training slots under a federally-funded research training grant awarded to Dr. Carolyn M. Mazure, as Principal Investigator.

This grant – called the Building Interdisciplinary Research Careers in Women’s Health, or BIRCWH – has provided the funding to establish a program to train exceptional junior faculty interested in a research career focused on women’s health and addictive behaviors. Funded through a $2.5 million grant, this training is available only to top-tier candidates who have earned an M.D., Ph.D., or equivalent and have already completed post-doctoral training.

Smith’s career goal, with the intensive mentoring and hands-on research training she is receiving through the BIRCWH program, is to flourish as an investigator focused on translating evidence-based research into prevention and treatment programs for diverse populations of pregnant women and mothers in community settings and in collaboration with community partners.

Her main research interests include the prevention of mental illness and promotion of mental health in children and families, and among pregnant and parenting women, in community settings. The basis of her work, she said, is the belief that, in addition to biological causes, illnesses are related to the social, cultural, historical and economic context in which individuals and families live.

“She work involves a true collaboration in and with the community to learn what’s needed to help women make positive changes,” Mazure said of Smith’s project.

“Many of the struggles of mothers in the community, including depression and smoking, occur together and have to be targeted in a coherent approach,” she said. “The knowledge that Dr. Smith and the community gain from this research will be translated into improved health for mothers and children.”

Women are at the highest risk of developing mood and substance use disorders during their reproductive years, according to Smith. While CDC data show that approximately 13 percent of women nationwide smoke during pregnancy, this figure is believed to be higher in impoverished communities where young mothers may be dealing with several major health and socio-economic problems at once, including depression, substance abuse, poor living conditions, unemployment – even homelessness.

In addition, Smith said, low-income, racially and
ethnically diverse women are the most likely to be adversely affected by mental illness. Moreover, mothers who have mental illness are more likely to have children who develop mental health disorders. Smoking addiction often accompanies such disorders, especially depression.

Smith has designed and initiated her community-based research with these potentially confounding factors in mind.

Her primary project in the research training program is a population-based study examining the effects of maternal smoking before birth on the cognitive, emotional and motor development of children 4 and 8 years old. As part of her study, she will examine several factors that could influence the outcomes, including the mothers’ mental health, prescription drug use and socio-economic situation while pregnant and after birth.

Smith’s secondary project, which complements the primary study, incorporates the training on addictions research into the development of evidence-based interventions to treat substance abuse and depression among the most at-risk pregnant and parenting women in community settings. She is in the process of introducing her pilot interventions in local neighborhoods.

In this secondary project, she is Principal Investigator under a grant from the U.S. Department of Health and Human Services Office of Women’s Health that the City of New Haven received through Yale School of Medicine. Smith describes this project, called the New Haven Mental Health Outreach for Mothers – MOMS – Partnership, as “bringing mental health services to mothers where they are.”

These interventions will be delivered through a partnership that includes Yale, the City of New Haven and its housing authority and health department, The Community Foundation for Greater New Haven, and several other non-profit community organizations.
Gesell Professor in the Child Study Center and Professor of Epidemiology, and of Pediatrics. Yonkers is Professor of Psychiatry and of Obstetrics, Gynecology, and Reproductive Sciences, Lecturer in Epidemiology (Chronic Diseases), and Director, PMS and Perinatal Psychiatric Research Program.

“What has been wonderful about the BIRCWH Scholar program is the opportunity to learn from accomplished scientists and conduct my own research with their guidance,” Smith said. “This is helping me move fully into the community of researchers on women’s health and addictions.”

Q. & A. with BIRCWH Scholar
Dr. Megan V. Smith

Q: How will your training as a BIRCWH (Building Interdisciplinary Research Careers in Women’s Health) Scholar help you achieve your goal of becoming an interdisciplinary researcher on women’s health?

A: Although I have worked in the area of perinatal mental health for several years, I have focused on mood and anxiety disorders, specifically depression and post-traumatic stress disorder. Training in substance abuse and other addictive behaviors offered through the BIRCWH provides me with the didactic learning, mentoring and research support necessary to fulfill my career goal of becoming an independent investigator in the area of community partnered research on perinatal mental health. Specifically, the interdisciplinary training and mentorship received through the program have supported my efforts to merge several fields of interest into a cohesive research program. I am fortunate to have two dedicated mentors, Drs. Mayes and Yonkers. Through weekly meetings and almost daily communication, they have provided explicit mentorship in the form of encouragement, problem-solving, networking opportunities and feedback, and implicit mentorship through role modeling as women scientists at the top of their fields.

Q: Could you describe how the two major projects you designed and initiated as part of your training complement each other?

A: The first project, an examination of the effects of mothers’ prenatal cigarette smoking on children exposed in utero, allows me to obtain firsthand experience administering and analyzing questionnaires and assessments pertaining to substance use in the perinatal period. We are developing innovative methods to measure the effects of in utero exposure on children (e.g. computer-based cognitive assessments). The secondary project allows me to translate the aforementioned skills and associated findings derived from a laboratory environment to “real-world” community settings.

Q: Why is your research involving the struggles of pregnant and parenting women focused especially on impoverished community settings?

A: Low-income women have high rates of depression and addiction and face a number of unique barriers that can prevent them from receiving treatment. Importantly, among women receiving state or federal cash assistance, mental illness has been identified as a significant barrier to successfully moving from welfare to working and living independently. Beyond depression and addiction’s direct impact on a woman’s psychological functioning, the long-term effects on her children’s development can be significant. Given that depression and addiction remain undertreated and underdetected among low-income pregnant and parenting women, the research I am engaged in is novel and exciting in its potential to reach large numbers of women. Partnering with community organizations, clinicians, and the mothers themselves to design and implement evidence-based interventions in novel community settings, in my view, offers a powerful combination to reduce disparities in mental health care and prevent the transmission of mental illness across generations of families.
Nearing a $50 Million Milestone

A key measure of our research center’s success is the external funding our scientists obtain using the results of the pilot studies we fund with your support.

Since we began in 1998, we have awarded more than $4.3 million in Pilot Project Program grants to Yale investigators and their results have generated just over $49 million in new external grants to further their research on women’s health – a testament to the strength of their work!

In fact, nearly 60 percent of our funded researchers obtain external grants – more than double the success rate for National Institutes of Health grant applications.

Our Success Starts With Your Support

Donors tell why they give to Women’s Health Research at Yale...

❖ “To continue leveraging investments in research to benefit women’s health.”
  – Jana Shea, Guilford, CT

❖ “You do such wonderful work – scientific research, explanations and information to the community – all wonderful, all needed.”
  – Cis Serling, Hamden, CT

We Need You NOW

As Chair of our Center’s Philanthropy & Communications Committee, I am proud to be a cheerleader for giving. Your contribution makes a difference!

Please consider directing all or part of your philanthropic giving to Women’s Health Research at Yale.

Whether you are considering a Yale reunion class gift, a donation through a non-profit organization like the Community Foundation for Greater New Haven, or a contribution that your employer or another organization may match – you can choose Directed Giving to support Women’s Health Research at Yale.

Another way to become a partner in the success of our center and improve the health and status of women is through Planned Giving. Options include a legacy gift, charitable gift annuity, charitable remainder trust or a gift of appreciated property.

Gifts from foundations, corporations and individuals make a difference. Your gift insures our place as THE nation’s premier center for propelling new discoveries on women’s health and translating them as quickly as possible into clinical practice.

The forecast for federal funding for health research is that it will be cut. Private contributions matter now as never before, as we continue on our path to improved health for women. This is not a time to hesitate. We need your help now.

Thank you!
Council News...
New Council Member Patricia Zandy

Patricia Zandy, J.D., who retired from Yale University in December after 20 years of service, has joined our advisory Council. She earned her bachelor’s degree from Molloy College in Rockville Centre, N.Y., and her law degree from St. John’s University in Queens, N.Y. After practicing law in New York, Pat came to Yale in 1990 and quickly became a key member of the Office of Development. She rose to Director of Principal Gifts, directing the cultivation and solicitation efforts involving the University’s most generous donors. Patricia was then named Associate Secretary of the University and Director of Corporation Affairs. In these posts, Patricia served as the principal deputy to the Vice President and Secretary on corporate governance matters, and served as primary manager of all work product and communications with the Yale Corporation. Her retirement from Yale is our gain, and we welcome her experience, talent and energy.

Council Charts Course for Major Growth While Taking Fond Look Back

Women’s Health Research at Yale’s advisory Council and staff met December 1st for a strategic planning session and pre-holidays dinner. Director Carolyn M. Mazure, Ph.D., presented a tribute to Kitty Friedman as she stepped down as Council Chair. Council members recalled specific moments that inspired them and strengthened their relationship with Women’s Health Research at Yale. Roslyn Milstein Meyer, for example, remembered Geraldine Ferraro’s brilliant keynote speech at our “Conference 2000 – Factoring in Gender.” Susan Katz recalled hearing at our 5-year celebration about what our funding had meant in fostering the careers of women’s health investigators. Lynne Schpero said her daughter quit smoking after the two heard one of our funded investigators discuss research findings at our 2002 conference.

At the December meeting, Council members shared ideas for ensuring our center’s growth and sound financial footing. Attendees discussed the progress of ongoing Annual Appeal and plans for a long-term endowment, and explored ways to expand community outreach efforts to educate and inform the public about the practical value of our scientific research.

Press Notes...
Why Our Research on Gender-based Smoking Cessation Really Matters

Ever wonder if smoking cessation programs, anti-smoking advertising campaigns and bans on smoking in public places make a difference? Take a look at the latest lung cancer rates.

The Centers for Disease Control and Prevention’s most
In the News

recent report on lung cancer rates shows a continuing decline among men and a *first-ever decline among women in selective U.S. locations* after decades of steady increase. The decreases, which can be seen as early as five years after smoking rates decline, correspond closely with smoking patterns and quitting rates across the country.

Cigarette smoking causes most lung cancer deaths in the United States, and lung cancer is the leading cause of cancer mortality among both women and men. Nationwide, according to the CDC, approximately 1 of every 5 adults smokes (23 percent of men and 18 percent of women).

The CDC report, which garnered modest media attention when it was released last year, noted that from 1999 to 2008 lung cancer rates among men decreased in 35 states and remained stable in nine others. During the same period, lung cancer rates among women decreased in six states, remained stable in 24 states and increased slightly in 14 states. Only in 2006 to 2008, did lung cancer rates among women decline nationally for the first time in decades, due primarily to a decrease in the lung cancer rate among women in California, the nation’s most populous state.

Having repeatedly pointed out our Center’s ongoing research on creating smoking cessation approaches tailored to the particular needs of women, I want to emphasize two important points that in my view are emphatically affirmed by the CDC report. One, women have a tougher time than men quitting smoking, and thus need smoking cessation programs that account for how women smoke for different reasons than men – to manage their moods and control their weight, for example. And two, greater investments in effective tobacco control strategies mean larger reductions in smoking rates and, thus, fewer lung cancer cases and greater savings in both lives and health care costs.

California, the state with the longest-running tobacco control programs, has cut its smoking rate almost in half, to about 12 percent, since 1988. In that year, voters approved using money from tobacco taxes on aggressive tobacco control strategies. The lung cancer rate in California is declining about *three times faster than in other states*, and the state has saved $86 billion in health care costs by spending $1.8 billion on anti-smoking programs, according to the CDC.

The sooner we design and implement effective gender-sensitive smoking cessation programs, and invest nationwide in tobacco control strategies, the better – for everyone.

Upcoming Workshops...

*Department of Psychiatry,*  
*Division of Women’s Behavioral Health – Annual Grand Rounds*

“Estrogen and Cognition”

Visiting Speaker:
**Pauline Maki, Ph.D.**  
Professor Psychiatry & Psychology  
University of Illinois at Chicago

Friday, May 25, 2012 from 10:15–11:45 am  
CT Mental Health Center, Auditorium  
34 Park Street, New Haven CT

Dr. Maki received her Ph.D. in experimental psychology from the University of Minnesota. She has a longstanding research interest in the effects of sex hormones on cognition, mood, brain function and psychological well being in young, midlife and elderly women. Her research using brain imaging led to new insights into the neural targets of hormone therapy in postmenopausal women.

*Stay current with WHRY!*  
Search these sites for “Women’s Health Research at Yale” to read daily health and research news!
February is American Heart Month!

Women and Cardiovascular Disease

For information on ways to reduce your risk, visit the “Community” section on our homepage.

www.yalewhr.org