In This Issue:

• **Current Research:**
  - Creating Nanoparticles to Combat Ovarian Cancer ...3–5
  - Adolescent Video Game-Playing: A Surprising Gender Difference.................6–8

• **Advancing Women’s Health Research at Yale - Options for Planned Giving** ........ 9

• **In the News..........................10–11**

*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 about our program please visit our website at:

➤ www.yalewhr.org

or email us at:

➤ WHResearch@yale.edu

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**Continuing Support:**

**Making a Critical Difference**

*Women’s Health Research at Yale* is extremely pleased to announce the renewed support of The Seedlings Foundation. Our program thanks the foundation for its continuing commitment in recognition of the scope and impact of our work. This support is making a difference in building our program’s research across critical areas of women’s health.

This ongoing partnership is essential to continuing the four major components of our program’s activities.

First, it helps propel innovative research through our Pilot Project Program, which provides “seed” money to promising investigations. Larger external grants from major funding agencies cannot be obtained without the feasibility data generated by these pilot projects.

Second, the renewed support allows us to continue developing our own research projects, such as a current investigation of post-deployment readjustment to civilian life for women veterans returning from combat zones.

Third, the foundation’s support enables us to inform the community of our research findings through our educational outreach - Initiative for Community Wellness. Finally, it allows our program to teach and mentor students and fellows pursuing research in areas of women’s health.

With The Seedlings Foundation as our partner, *Women’s Health Research at Yale* will continue to generate important findings on women’s health to improve the well-being of all.

“The generous philanthropic efforts of The Seedlings Foundation will help us ensure the long-term sustainability of our program,” said Dr. Carolyn M. Mazure, Director of *Women’s Health Research at Yale*. “We are very grateful for the foundation’s support, as it allows our program to continue to pursue forward-looking investigations that significantly inform women’s health and shape a larger movement toward better health and healthcare.”
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 in support of both the endowment fund and annual general operating costs for research and education are welcome at all levels.

To join the Society of Friends visit www.yalewhr.org or mail your gift to Women’s Health Research at Yale P.O. Box 208091 New Haven, CT 06520-8091

Gifts were made to Women’s Health Research at Yale on behalf of the following people.

In honor of...
Mary Arnstein • Susannah Bailin • Alice Bottone
Pamela Ehrenkranz • Congresswoman Rosa DeLauro
Drs. David & Lynn Fiellin • Susan Katz
Eileen Kraus • Carolyn Mazure • Roslyn Meyer
Patricia Russo • Phyllis Seton
Betty Sussman • Rebecca Younger

In memory of...
Professor Sylvia Ardyn Boone • Betty Sacher
Katharine Lustman Findling

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

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Many women with ovarian cancer respond fully to the traditional combination of surgery and chemotherapy. But the cancer often recurs and the tumors in the majority of these patients are resistant to drugs. As a result, women with ovarian cancer suffer the highest mortality rate among patients with gynecological cancers.

With this reality in mind, researchers are seeking new, effective ways to treat recurrent and resistant ovarian cancer.

Enter a team of Women’s Health Research at Yale-funded researchers who are attempting to develop a new strategy by bridging the gap between life science and materials science. The investigators assembled for this WHRY Pilot Project Program study are combining recently acquired knowledge of the molecular genetics of ovarian tumors and their vulnerabilities, with the use of nanoparticles — the latest biomedical engineering technology for targeting these tumors and delivering chemotherapy.

The team plans to use these ultra-tiny particles as homing devices to seek out and strategically bind to ovarian tumors. These nanoparticles, made of nontoxic biodegradable materials, are designed to pinpoint the cancer cells and infiltrate the most drug-resistant tumors to deliver potent substances to destroy them. Such a treatment, if successful, could significantly improve survival rates for ovarian cancer.

Conceptually, this idea sounds elegantly simple. But it has taken years of clinical know-how, medical discovery, and technological innovation for the members of this interdisciplinary team to begin to carry out their aim.

“Our goal is to try to kill the disease in a completely different way,” said Dr. Alessandro Santin, the lead investigator.

A Professor of Obstetrics, Gynecology and Reproductive Sciences, Santin combines clinical experience with extensive knowledge of the intricacies of ovarian cancer cells, gained through practice as a physician and as a researcher funded many times by the National Institutes of Health and private foundations. A native of Italy who joined the Yale faculty in 2008, Santin won the Italian Society of Gynecologic Oncologists Award for Translational Science and the Young Investigator Award from the American Association of Cancer Research.

In previous work, Santin and his laboratory team analyzed genetic fingerprints of ovarian cancer cells and discovered extremely high expression of the genes for making two particular proteins, claudin-3 and claudin-4. (Gene expression is the process by which information from a gene is used to make proteins, the building blocks of cells.)

These two proteins, according to Santin, happen to be the receptors — on the surface of cells that line the ovaries — for a potent bacterial poison found in nature, a common cause of food poisoning called Clostridium perfringens enterotoxin, or CPE. Most ovarian cancers are in the lining of the ovaries, and these ovarian tumors have high levels of these two particular proteins. Thus CPE can be an effective targeting agent and destroyer of ovarian cancer cells. Unfortunately, intravenous delivery of CPE is toxic.
However, Santin and his laboratory team hypothesized that a part of the “binding” area of CPE, a protein fragment or peptide, could be used to target ovarian cancer cells. Importantly, this fragment is not toxic but has sufficient affinity for sticking to the target receptors, claudin-3 and claudin-4, of the ovarian cancer cells. Santin recognized that, with these characteristics, this CPE peptide held promise as a safe means to find and lock onto ovarian cancer cells. Santin and his laboratory team published these findings last July in the peer-reviewed journal *BMC Cancer*.

Not long ago, Dr. W. Mark Saltzman, Yale’s first Chair of Biomedical Engineering, and Santin had discussed the possibility of establishing an interdisciplinary team at Yale to work on developing various anti-cancer technologies, including the use of nanoparticles. Saltzman has been designing and making nanoparticles for other applications, including treatment of other types of tumors, for more than a decade.

Their conversations led them to collaborate on the current WHRY pilot study – their first joint project. “We’re very pleased to be able to work together,” Santin said of his collaboration with Saltzman. “This project combines cutting-edge bioengineering work with our translational research.”

In recent months, Saltzman has been busy developing the nanoparticles for this project. A longtime biomedical engineer who has written textbooks on engineering for improving drug delivery, much of his work has focused on creating biodegradable materials and nanoparticles.

The Iowa native joined the Yale faculty in 2002, when he was appointed the Goizueta Foundation Professor of Biomedical Engineering, and Professor of Cellular and Molecular Physiology and of Chemical Engineering. He earned his Ph.D. from MIT in a program that combined study of medicine at Harvard with study of engineering for advancing medicine. He won numerous awards for his teaching and research, first at Johns Hopkins and then at Cornell.

Before coming to Yale, Saltzman was part of an interdisciplinary team that developed what is now the standard of care for treating the most aggressive forms of brain tumors: biodegradable wafers that contain chemotherapy drugs. Called Gliadel® wafers, surgeons place them during brain surgery at the site where a tumor has been removed, and then close up the cavity. The wafers work by slowly releasing the chemotherapy drug into brain tissue over a period of days and weeks; the wafers dissolve over a period of months. Available for routine clinical use since 1996, this was the first new treatment for brain tumors approved by the FDA in 25 years.

While the Gliadel® wafers are the size of a dime, the biodegradable nanoparticles Saltzman has created in the WHRY pilot study for use against ovarian cancer are so small that 100,000 of these nanoparticles could fit across the diameter of a dime.

But it is not just the size of the particles that matters. “The details of the design matter,” Saltzman said.

Each nanoparticle is formulated to have thousands of spikes protruding from its surface, like Velcro fibers, to maximize the capacity for attaching to tumor cells. These specially designed nanoparticles can be coated with the peptide “homing device” on the spiked surface, and can carry a potent chemotherapy as cargo inside the nanoparticles. The binding activity of the peptide can allow the chemotherapy to breach the defenses...
of the otherwise drug-resistant tumor. Moreover, the chemotherapy agent can be unleashed in the tumors only when the nanoparticles hit their targets, not before. This could keep the treatment from destroying healthy cells – a problem that is common in cancer therapy – and could minimize unwanted side effects.

The first steps in the ovarian cancer pilot study were to formulate the nanoparticles with the peptide and determine, using a fluorescent dye as a tracer, whether they can find and lock onto the target tumors, and deliver selected chemotherapy agents. The investigators’ aim was to carry out this first step using samples of chemotherapy-resistant ovarian cancer cell lines donated by patients.

Santin is pleased to report that these first pilot project aims have been met. The results show higher rates of binding with ovarian tumors by the peptide-coated nanoparticles, compared to rates of binding by nanoparticles without the peptide. This demonstrates that the CPE-laden nanoparticles are selectively hitting and sticking to their intended targets.

The investigators are now working on the study’s final step, which is to determine whether the specially formulated nanoparticles can have the same kind of success in animal models of chemotherapy-resistant ovarian cancer cells. The study is utilizing female mice, helping to ensure that results are as clinically relevant as possible. (Although it seems only natural to use female animal models when investigating an area of women’s health, this is not always done in science.)

Santin and Saltzman said the data produced so far are encouraging. Using these preliminary results, the two scientists already have applied for funding from the National Institutes of Health to conduct a further, larger study, with the goal of carrying out clinical trials as early as two or three years from now. This would be an unusually accelerated timetable, given the considerations and approvals required in translating a discovery like this into a treatment.

The ultimate goal of the pilot study and the anticipated further investigations is to someday use the nanoparticles coated with the homing peptide as "microscopic shuttles," as Santin describes them, to carry a tumor-killing toxin to the targeted ovarian cancer cells of patients suffering from chemotherapy-resistant cancer.

One possibility, according to Santin, is to harness the cell-destroying capacity of diphtheria toxin by encapsulating a plasmid, or gene molecule, of this bacteria within the nanoparticle. The package would act as a tiny smart bomb encoded with the genetic sequence to switch on the diphtheria toxin only when it hit the intended target, avoiding healthy cells but lethal against ovarian tumors – a real-life magic bullet.

Perhaps, as Saltzman likes to say, scientists do not need to develop better drugs, just better ways to deliver them.
Playing video games has become pervasive in the lives of American teenagers, and many parents wonder if the hours their children spend playing these games can have ill effects.

A new study led by Women’s Health Research at Yale-affiliated investigators Drs. Rani Desai and Marc Potenza is among the first and largest to examine possible health links to video gaming in a sample population of adolescents. The study grew out of work that the two investigators conducted with WHRY’s interdisciplinary research core on Addictive Behaviors.

This new research indicated that most teens appear to be playing video games without associated problems, yet video game playing does appear to be problematic in a small segment of teens.

The teens surveyed for the study were asked how much time they spent at their video game consoles or computers. But the frequency of play was not included in the definition of problematic gaming. “While some problem gamers may in fact spend more hours playing, the hallmark of problematic gaming is an inability to resist the impulse to play,” Desai said.

The results of the survey suggest that the small segment of teens with problematic video gaming – boys and girls – are more likely to also be engaged in other risk behaviors such as smoking cigarettes, using illegal drugs and getting into serious fights, according to Desai, Associate Professor of Psychiatry.

The findings come from an anonymous questionnaire that surveyed the video-gaming habits of 4,028 Connecticut high school students ages 14 to 18, during the 2006-2007 school year.

**Expected and Unexpected Gender Differences**

The study was published in November in the journal *Pediatrics*. Desai’s co-authors included Potenza, Professor of Psychiatry, and Dr. Suchitra Krishnan-Sarin, Associate Professor of Psychiatry.

The investigators were not surprised to find that video game playing is much more prevalent among boys. According to the study, 76.3 percent of boys said they played at least one hour per week, while only 29.2 percent of girls played as much.

But the investigators were surprised to find a previously unknown gender difference. Boys who play video games are not more aggressive than non-gaming boys, the study showed. However, girls who play video games are more likely than other girls to get into serious fights and carry a weapon to school, according to the findings.

Desai cautioned against drawing conclusions about whether the playing of video games is making some girls more aggressive.

The study was not designed to say whether playing video games can cause harm. This would
require information on health behaviors before and after the playing of video games started. Rather, this population survey represents a first step in understanding whether the activity is even associated with unhealthy behaviors, and the breadth and nature of the possible associations.

“There are not many good studies of whether video gaming is associated with negative health behaviors in kids, or of how many kids might be involved with problematic video gaming,” Desai said. “These questions formed the genesis of our study.”

Overall in the population surveyed, “We found practically no association between gaming and negative health behaviors,” Desai said. “However, a small but not insignificant proportion of teens are unable to control their gaming,” Desai said. This becomes a cause for concern because the inability to resist playing is associated with other problem behaviors.

Both Desai and Potenza have a special interest in understanding behavioral problems called impulse control disorders. Although not labeled as addictions, these disorders occur when a person becomes very involved, to the point of obsession, with a particular behavior, such as gambling or shoplifting. Loss of impulse control may also be seen in internet use or shopping. The researchers have investigated problem and pathological gambling, and lately have been trying to assess whether patterns of adolescent video game playing have the hallmark signs of an impulse control disorder.

Of the high school students surveyed, 4.9 percent reported what the investigators call problematic video gaming. These teens had trouble cutting back on their gaming, felt an irresistible urge to play, and experienced tension that could be relieved only by playing. Boys were more likely to report problematic gaming (5.8 percent) than girls (3.0 percent).

Health Behaviors of Teens Without Problematic Gaming

The vast majority of boys who played video games, those without problematic gaming, earned higher grades than boys who did not play video games, the survey showed. The game-playing boys also were significantly less likely to smoke cigarettes, according to the survey. In addition, the boys who played video games were more likely to say they had never used alcohol or smoked marijuana.

The fact that video gaming in boys was linked to healthier behaviors and, more importantly, not linked to unhealthy behaviors, may mean simply that, for boys, the playing of video games is part of mainstream young male culture.

The girls who played video games, those without problematic video gaming, also were less likely to smoke marijuana and drink alcohol. Video game playing among the girls did not appear to be associated with higher or lower grades, according to Desai. Finally, the game-playing girls were less likely to report feelings of depression, but there was no such association among boys, Desai said.

Not enough is known about recreational vs. problematic levels of video gaming, according to Desai. The next research step, she said, is to determine safe levels of gaming (levels that are not significantly associated with problem behaviors) and to identify risk factors for problematic gaming, and strategies to prevent problematic gaming. In addition, video gaming researchers need to know
more about the potential beneficial uses of video games, given their wide popularity among youth.

Most previous studies on youth video gaming have focused primarily on whether there is a link between aggression and video gaming in children who play very violent games, and large multi-player online games. The literature in this area is inconsistent.

The most popular video games span a variety of genres and ratings and include non-violent dancing, puzzle, and car racing setups, as well as violent shooter and warfare scenarios. Driving and car racing games appear to be among the most popular of all, according to a 2008 report by the Pew Research Center.

Desai cautioned that the recent rise in popularity of the Wii™ system, by Nintendo®, may have partially redrawn the video gaming landscape. That might mean that research into new gaming habits is needed to stay abreast of the changing behavior among children.

Investigator Profiles

Rani A. Desai, Ph.D., M.P.H., is Associate Professor of Psychiatry and of Public Health (Health Policy). She received both her M.P.H. in chronic disease epidemiology, and her Ph.D. in mental health services research and psychiatric epidemiology from Yale. Dr. Desai is head of the Women and Trauma Core of Women’s Health Research at Yale, and is Associate Director of the Robert Wood Johnson Clinical Scholars Program at Yale. She also serves as Associate Director of the Northeast Program Evaluation Center, the evaluation arm of mental health services for the U.S. Department of Veterans Affairs, and as Director of the Evaluation Division of the National Center for PTSD, post-traumatic stress disorder.

Dr. Desai is the lead investigator in a study to determine whether there are gender differences in post-deployment readjustment to civilian life for combat veterans returning from Iraq and Afghanistan. Women’s Health Research at Yale and the VA are collaborating on this study, which is funded by a VA grant that grew out of a WHRY pilot study. This study will be featured in a forthcoming edition of our newsletter.

Marc N. Potenza, M.D., Ph.D., is Professor of Psychiatry, in the Child Study Center and of Neurobiology. He received both his M.D. and his Ph.D. from Yale. His research focuses on how non-substance (“behavioral”) addictions are similar to and different from substance addictions. He uses brain imaging, genetic, clinical, pharmacological, behavioral and epidemiological approaches to study this topic. He is also interested in how individual differences related to impulsivity and gender, for example, influence non-substance and substance addictions. Among his posts, Dr. Potenza is head of the Women and Addictive Disorders Core of Women’s Health Research at Yale, and Director of the Problem Gambling Clinic, and Center for Excellence in Gambling Research.
A key challenge in raising vital gifts to sustain Women’s Health Research at Yale is the widely held assumption that Yale programs do not (or should not) need financial support. However, our program is self-supporting, meaning we must raise our own funds to support innovative research that benefits women’s health.

Please Consider a Planned Gift

One way to ensure that our research continues is Planned Giving. Such giving involves a set of tools that WHRY can make available to donors that may enable them to make larger gifts than they ever thought possible. *Options include:

- **Legacy Gift** - as simple as leaving a dollar amount or percentage of your estate to WHRY in a will or trust. It can also include naming WHRY as the beneficiary of a life insurance policy or remaining funds in a retirement plan or IRA.

- **Charitable Gift Annuity** - a gift of cash or securities to WHRY, resulting in a lifetime annuity for the donor, or income stream for a loved one.

- **Charitable Remainder Trust** - a trust of securities which will pay income to the donor or loved ones for a number of years, with the remainder at the end of the term of the trust gifted to WHRY.

- **Gift of Appreciated Property** - giving stocks, bonds, or mutual funds that have appreciated in value, thus avoiding taxes on built-in capital gains.

These kinds of gifts allow donors to carry out forward-looking intentions to ensure Women’s Health Research at Yale continues to improve health for future generations of mothers, daughters and sisters. Here is why some of our donors say they give:

> “Women’s health research is the most important way to help create a healthy community and country.”
> - Mrs. Edward Petriuolo Jr. (New Haven, CT)

> “Your pioneering and science-based additions to the knowledge and practice of women’s health.”
> - Robert & Margaret Patricelli Family Foundation (Simsbury, CT)
In the News

Council News...

Kitty Friedman in New Development Post

Marjorie “Kitty” Northrop Friedman, J.D., Chair of our advisory Council, has been named Director of Gift Planning at The Ethel Walker School in Simsbury, CT. An attorney, Kitty previously was an Associate at Holland & Knight LLP in New York City. She is a graduate of Bates College and Vermont Law School.

Patti Russo Becomes Women’s Campaign School President

In December, Patti Russo, Chair of WHRY’s Philanthropy & Communications Committee, was elected President of the Women’s Campaign School at Yale. It is the only non-partisan campaign training school for women in the country. Each year, the school holds a week-long summer session to prepare women for political leadership positions. Alumnae include U.S. Senator Kirsten Gillibrand (N.Y.), U.S. Representative Gabrielle Giffords (Ariz.) and Tulsa, Oklahoma Mayor Kathy Taylor.

Russo Honored by Italian-American Women’s Organization

Patti Russo was in the news again in January, when the CT Region of the National Organization of Italian American Women (NOIAW) recognized her as an exceptional leader and role model. Patti was honored as one of Three Wise Women at the organization’s second annual Epiphany Celebration, held January 30th at the New Haven Lawn Club. Congresswoman Rosa L. DeLauro, a longtime champion of advancing women’s health research, presented the awards. Founded in 1980, NOIAW is the nation’s premiere leadership organization for women of Italian heritage.

Press Notes...

The Need for Science Literacy

As the Press Officer/Science Writer for our program, one of my favorite duties is to translate complex information about our research into language that everyone can understand.

At a minimum, making the work of our scientists easily digestible helps WHRY’s friends and supporters become more knowledgeable consumers of health information, and helps propel the cause of health equity for women – by themselves fundamentally important goals. But I view our program’s educational outreach as part of a larger mission.

Many Americans lag in science literacy. On average, American students rank well below students in other countries in math and science.

If we are, as President Obama says, facing our generation’s “Sputnik Moment,” we must all act as ambassadors for increasing science literacy.

Community Events...

Dr. Mazure Speaks to Science Journalists...

Our Director spoke to science journalists on November 7th, as Yale hosted the National Association of Science Writers annual conference. A group of attendees chose in advance to hear Dr. Mazure’s lecture on women’s health and our program’s research efforts. Journalists and organizers remarked at the close of the conference that the talk was among the highlights of the event.

Science News Magazine Interviews Our Director...

Erika Engelhaupt, Deputy News Editor at Science News magazine, who was in the audience for the November 7th presentation, interviewed Dr. Mazure in December about some of her latest...
research on the relationship between the menstrual cycle and smoking cessation outcomes. The interview is expected to be part of a forthcoming piece in the magazine concerning various aspects of women’s health.

**Dr. Mazure Presents Grand Rounds Lecture at the Yale Cancer Center...**

...WHRY Director Mazure spoke about the advantages of studying women’s health and gender differences during a Yale Cancer Center Grand Rounds lecture on January 11th. Dr. Thomas Lynch, Director of YCC, introduced Dr. Mazure to a packed auditorium. Dr. Mazure explained the importance to care-givers and researchers of looking at health outcomes by gender and considering gender-specific prevention strategies. She also described some of our program’s ongoing studies that focus on various types of cancer; several of these Pilot Project studies have joint funding from WHRY and the Yale Cancer Center.

**Training the Next Generation of Researchers**

A key mission of our program is to teach students who want to pursue research in women’s health and gender differences.

Interviews are under way for the selection of junior faculty scholars who will be trained to conduct interdisciplinary research on addictive behaviors in women.

More than 20 applicants, half from Yale, are vying for four positions to be filled this summer in the Building Interdisciplinary Research Careers in Women’s Health (BIRCWH) Scholar Program, funded by a National Institutes of Health grant to the Department of Psychiatry.

Our Director, Carolyn M. Mazure, Ph.D., is partnering with Samuel A. Ball, Ph.D., Professor of Psychiatry, on this NIH Faculty Training Grant.

**Workshop Series...**

**Upcoming Presentation:**

**Friday—May 13, 2011**
Department of Psychiatry Grand Rounds—Sponsored by the Women’s Behavioral Health Research Division

**Depression & Heart Disease: Is There Gender-Specific Risk?**

Visiting Speaker: Viola Vaccarino, M.D., Ph.D.
Professor, Rollins School of Public Health, Department of Epidemiology, Director, Cardiovascular Outcomes Research & Epidemiology, Emory University

Time: 10:15-11:30 am
Location: CT Mental Health Center—Auditorium 34 Park Street, New Haven (CT)

We believe social media applications play a key role in our outreach.

Join us on Facebook and Twitter and stay up to date on our workshops, events, and news.
Our Newsletter has Gone Green!

The print version is not going away, but if you would like to receive our newsletter online please contact us at whresearch@yale.edu