Using Particles That Are Smaller Than the Head of a Pin to Treat Cancer

Patients with high-grade ovarian cancer and uterine serous cancer (USC) often respond well to surgery and chemotherapy. At first.

But these can be highly aggressive tumors that often spread into the space within the abdomen known as the peritoneal cavity. According to a recent study, one rare but aggressive type of uterine cancer is propelling an increase in deaths from the disease in the United States, particularly among Black women.

Moreover, resistance to chemotherapy often develops, and the disease recurs. This results in ovarian cancer causing more deaths than any other cancer of the female reproductive system.

For one possible treatment, clinical trials demonstrated the effectiveness of injecting a drug known as epothilone B (EB) into the abdominal cavity, targeting tumor cells that have grown resistant to standard chemotherapy medications. However, the drug’s high toxicity when delivered this way causes severe side effects, preventing further use.

Now, thanks in part to research begun more than a decade ago with funding from Women’s Health Research at Yale, our colleagues are closing in on a way to deploy effective cancer-fighting medication safely with the help of nanoparticles. © Anthony DeCarlo

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Using Particles... (Continued from front cover)  
medication safely with the help of ultra-tiny non-toxic biodegradable objects known as nanoparticles. Developed by Dr. W. Mark Saltzman, the Goizueta Foundation Professor of Biomedical and Chemical Engineering, these nanoparticles have organic chemicals on their surface that allow them to stick to cells in the abdominal cavity so they are not cleared from the area before they can do their job.  

“With bioadhesive nanoparticles, we can safely entrap a drug and deliver it so it slowly releases in a high concentration, directly to our target, over a long time,” Saltzman said. “By localizing the delivery of the drug, we are decreasing toxicity and increasing effectiveness.”  

With data funded through WHRY’s grant, Drs. Saltzman and Alessandro Santin, professor of obstetrics, gynecology, and reproductive sciences, secured funding from the National Institutes of Health to demonstrate the safety and efficacy of this technique in a model system, publishing their results in 2016. Saltzman then partnered with Dr. Michael Girardi, Evans Professor of Dermatology, to develop a non-surgical treatment for skin cancer using injections of nanoparticles carrying a chemotherapy agent. In a paper published last year, they demonstrated the capacity for this method to bind to the tumors and kill a significant number of cancer cells. In addition, the treatment involves triggering an immune response to rid the body of cancer cell waste and respond against any remaining cancer cells.

Dr. Saltzman and Girardi founded a company called Stradefy Biosciences, which has licensed patents to this technology from Yale, while continuing to develop these techniques for clinical use. Dr. Nita Ahuja, William H. Carmalt Professor of Surgery and chair of surgery, serves as an advisor for abdominal cancer applications. “We are thrilled that the work we sponsored many years ago continues to produce such varied applications for serious health concerns,” said WHRY Director Carolyn M. Mazure, PhD. “This is the model for how investing in Yale’s most innovative and collaborative individuals can produce steady progress that will improve and even save lives.”

Dr. Saltzman also used a WHRY grant to create a vaginal ring that provides contraception while protecting against sexually transmitted infections. Yale has filed a patent application on this unique ring design, and Saltzman continues to seek funding to further develop the product and possibly adapt it to treat endometriosis.

“The type of funding WHRY provides is critical for the innovation-based work I do,” Saltzman said. “I could say, “We are going to make these particles with this unique property.’ But to get substantial buy-in from a company or the NIH, you need to have the data to demonstrate that this works. Early funding, particularly for collaborative projects with unproven technologies, is critical.”

ABOUT THE INVESTIGATORS  
Dr. W. Mark Saltzman received his PhD from Massachusetts Institute of Technology and his BA from Iowa State University. At Yale, he is the Goizueta Foundation Professor of Biomedical Engineering and professor of cellular and molecular physiology and of chemical engineering, affiliated faculty at Yale Institute for Global Health, and chair of the Department of Biomedical Engineering. His research is motivated by the desire to create safer and more effective medical and surgical therapies. He focuses on creating better methods for drug delivery. His group has developed technology based on the use of biocompatible polymers for the controlled delivery of drugs, proteins, and genes.  

Dr. Alessandro Santin graduated with honors and received his postgraduate training in obstetrics and gynecology at the University of Brescia in Italy. At Yale, he is professor of obstetrics, gynecology, and reproductive sciences and a clinical research program leader for the Gynecologic Oncology Program at the Yale Cancer Center. His current research focuses on immunotherapy for ovarian and endometrial cancer, developing vaccines against human papillomavirus (HPV), and the use of antibodies against chemotherapy-resistant gynecologic tumors.
A Q&A with Dr. Christine J. Ko

With a grant from Women’s Health Research at Yale, Dr. Christine J. Ko identified the absence of a common gene mutation in a form of skin cancer (squamous cell) frequently found on women’s legs. She is continuing to explore this as a promising biological marker to predict the growth rate and recurrence of these lesions. A professor of dermatology and pathology at Yale School of Medicine, she has been pursuing this work toward a clinical application while actively seeing patients. Recently, she wrote a book, published by Routledge, titled “How to Improve Doctor-Patient Connection.” We chatted with Dr. Ko to get her insight into the roles psychology and processes as related to diagnosis and treatment. Dr. Ko: Yes and no. It was difficult to organize the book in a coherent fashion, as initially I was not writing this as a doctor. I was writing it from a place of pain, as a mother whose son was misdiagnosed for too long, thinking: Is there a way that other people do not have to do as much as I did? Through writing the book, I realized that if I had known how to connect better as a doctor or as a patient advocate, I would have navigated the health care system better. Maybe I would have known how to get my questions answered in a way that I could understand, and maybe the doctors we saw would have had a better idea of what my son and I needed. I realized through the whole journey that it’s ultimately about personal connection. We just have to see people — doctors, patients, parents, children, friends, colleagues — literally and figuratively. And listen to them. Dr. Ko: I think many of us do not understand how we make decisions. If I intuitively make a certain decision, that is an example of System 1 processing. If someone asks why I like it, and I analyze and give reasons, that is an example of System 2 processing. The first is like a gut feeling. We react to interactions involving female patients? Dr. Ko: I don’t love the term “gaslighting” because it implies a deliberate, purposeful attempt to mess with my head. This is not necessarily the case. Doctors are medical experts, but patients are experts in their own experience. We need to trust each other more and listen to each other. Dr. Ko: If I were a female patient, and even more so if I were a female person of color, there is a higher chance that the doctor-patient relationship can be more damaging than it currently is. Doctors are human and have implicit biases like anyone else. With no blame on individual doctors, we have got to get better, and this includes system changes. But to start with, on the individual level, the doctor-patient relationship can be more damaging than it’s currently set up to be. Doctors are medical experts, but patients are experts in their own experience. We need to trust each other more and listen to each other. What role must female patients take to improve relationships with medical providers that can lead to better health outcomes? We need to trust you. Be aware of yourself. Why are you going to the doctor? Have that clear in your mind. Make sure that your needs are addressed. And tell the doctor if your needs are not addressed. As an expert in your own experience, you are deserving of respect. Ask when things do not feel right or sit right with you. A good doctor will be willing to listen.
Ke’ala Akau, ’22

This past fall, Ke’ala began coursework toward a master’s degree in public health as part of a five-year BA/BS-MPH program at the Yale School of Public Health. She is focusing her studies on social and behavioral sciences as well as social justice and health equity.

“As someone who wants to be a physician, I feel it is important to understand the social determinants of health,” she said. “How does history influence the factors that create health disparities?”

Last summer, she received a competitive grant for a fellowship with Downtown Evening Soup Kitchen in New Haven, working with Executive Director Steve Werlin. Her work included grant writing and tracking, developing a social media strategy, and contributing to and copyediting the nonprofit organization’s newsletter.

Ke’ala plans to take a gap year before attending medical school, possibly working with a community organization while conducting research.

“I’ve embraced what is known as community-based participatory research,” she said, noting how WHO operates with policy lab Elevate and its local collaborators. “It can be so helpful to involve community partners at every stage of the process, from choosing topics of study to analysis and dissemination of the findings.”

As a communications fellow with WHRY, she explored, in her research and writing for the blog, the importance of inclusive language and policies to increase access to menstrual products. While she does not know precisely where her career might take her, she imagines those skills will remain valuable.

“For physician leaders within health systems, communication is a big part of their role,” she said. “Whether talking to a patient in the clinic or making an announcement or making a case within the community. It’s important for people to have the information they need to make decisions about their health.”

Cecilia Crews, ’19

Cecilia just completed her first year as an MPH student at Columbia University’s Mailman School of Public Health in New York. She is spending the summer in Ghana to work on a research project evaluating a new emergency response system in the country’s northern region.

“My interests have changed a lot in public health over the years, definitely with the help of WHRY,” she said. “I’m interested in the systems that underpin these vertical programs, such as HIV treatment or malnutrition. With my degree, I want to create stronger health systems in countries working to expand beyond an aid relationship with the international community. Promote more sustainability in their health care system.”

Her experience helping WHRY incorporate sex-and-gender research findings into the medical school curriculum has continued to shape her thinking.

“This needs to be integrated into every single conversation,” she said. “Women’s health and the role that sex, gender, race, and ethnicity play in health. To better prevent and treat diseases and conditions, we need to understand social determinants of health.”

This summer will represent Cecilia’s second service-related trip to Africa. Before the pandemic forced her to return home, she was working as a maternal and child health volunteer with the Peace Corps in Rwanda. Even as her plans take her far away, her thoughts often return to her time with WHRY back home, working with WHRY Director Carolyn M. Maurer, PhD, and her mentor on the curriculum project, Dr. Njeri Thande.

“In women’s health sections of public health classes, we might learn facts about the state of women’s health and not necessarily feel empowered or optimistic that the world can change,” she said. “But at WHRY, I learned to be more than an advocate. They helped me see what needs to change and to take action.”

Nardos Kebede, ’20

As a WHRY fellow, Nardos Kebede worked in the behavioral neuroscience lab of Dr. Nii Addy, associate professor of psychiatry, focusing on sex-and-gender differences in the neurobiological mechanisms of depression and addiction processes. Following graduation, she spent the last two years in Dr. Addy’s lab advancing this work, including projects exploring sex differences in the effects of chronic stress exposure.

“Before my fellowship with WHRY, I had some exposure to how research was conducted,” she said. “But the fellowship, this extended period of time in the lab, and having mentors focused on the health of women has helped me to articulate what is lacking and what type of research I want to do.”

This August, Nardos will begin a PhD program in neuroscience at Emory University in Atlanta.

“Moving forward in my graduate school career, I definitely want to conduct studies where sex and gender are a main focus of analysis and not just a variable,” she said. “I’m glad to be in this field and that others are moving in this direction.”
Meet WHRY’s New Senior Program Manager

Jessica Quistorff has long felt drawn to improving the health of women. Her mother, a former Emergency Department nurse at St. Barnabas Hospital in Livingston, N.J., and health manager of the Head Start program at a public school district in Connecticut, demonstrated the value of taking care of others.

“IT’S NICE TO BE IN A PLACE WHERE EVERYONE KNOWS HOW WE GET THE JOB DONE.”

“She instilled that in us,” Quistorff said of herself and her two siblings. “I knew I wanted to help the community in some way.”

As Women’s Health Research at Yale’s new Senior Program Manager, Quistorff embraces the opportunity to help change medical research and care to better address the needs of women and explore sex-and-gender differences between and among women and men.

Jessica Quistorff saw WHRY as a unique chance to move closer to her family in the state while contributing to a mission she found perfectly aligned with her career goals.

Resiliency and give children the best possible foundation for health and happiness.”

Before joining Children’s National Hospital, Quistorff served as a research study specialist at Memorial Sloan Kettering Cancer Center’s Breast Medicine Clinical Trials Office in New York and earned her master’s degree in public health from Columbia University Mailman School of Public Health. She concentrated on sexual and sexual and reproductive health.

“We also studied ethics and how to avoid the missteps of the past, such as the persistence of racial disparities in healthcare and studies that have not properly served the health needs of marginalized communities,” she said. “It’s important to teach this history and engender proper values in the next generation of medical providers.”

A graduate of the University of Connecticut, she also saw WHRY as a unique chance to move closer to her family in the state while contributing to a mission she found perfectly aligned with her career goals.

“Women’s Health Research at Yale seemed like everything I had been working toward,” she said. “I could hardly believe my good fortune. I got to work in my field, continue to explore my passion for women’s health, and be closer to my family.”

And she is excited to continue making a difference in people’s lives.

“WHRY is such a passionate center with a practical mindset,” she said. “It’s nice to be in a place where everyone knows what tasks we must accomplish, that every step counts, and that this is how we get the job done.”

The Gift of Better Health

In 2013, Wendy and Tom Naratil, Yale Class of ’83, established an endowment for Women’s Health Research at Yale specifically to accelerate discovery through our Pilot Project Program.

Since the start of this valuable support, the Naratils have seen the annual pilot project seed grants they have underwritten achieve important developments in understanding cardiovascular disease, cancer, mental health, and more. These developments were made possible because WHRY’s Wendy U. and Thomas C. Naratil Pioneer Awards produced needed data to advance scientific discovery and demonstrate the feasibility of concepts that enabled our funded investigators to secure external grants capable of moving their work toward practical applications.

For example, Dr. Caroline Johnson’s Naratil Award allowed her to demonstrate how a very new, innovative technology — that shows us how our metabolic systems work — can trace the underlying digestive mechanisms behind a type of colon cancer that is deadlier in women than men.

Another Naratil Award-funded researcher, Dr. Kelly Cosgrove, in collaboration with Dr. Evan Morris, developed a new technology for imaging the brain that showed how tobacco smoking affects the brains of women and men differently in real-time and now is adapting it for understanding different brain effects of cannabis between women and men.

Other ongoing research launched with the Naratil Pioneer Award includes investigations into a better way to identify and treat types of heart attacks more likely to occur in women than men and how to promote psychological resilience in health care providers facing enduring stress and whether there are gender differences in response to stress.

“This work is so important,” Wendy Naratil said. “Tom and I like the fact that when we support research, the returns are often much greater than the initial investments. We recognize that advancing science is a slow process. Making headway can take a long time, but you need to take that first step.”

The Naratils have now established a new endowment, directed toward helping the center meet its annual operating expenses — a need Wendy recognized from her vantage point as an active member of the WHRY Advisory Council.

“On a very basic level, if you don’t support the day-to-day costs, the center cannot do all the wonderful things it does,” she said. “Not just filling the gaps in research on women’s health but preparing students and junior faculty members. Establishing the science behind effective health policies. Growing with the community to make a bigger impact on public health.”

Tom Naratil said people might not fully understand how necessary such gifts are for the success of WHRY. With only limited support from Yale School of Medicine, WHRY must raise funds from individuals and foundations every year to support its mission.

“I think when some people hear about a Yale program or center, they might assume it comes under the umbrella of the university’s tremendous resources,” he said. “In fact, WHRY is thriving because people understand its importance and are willing to fund it.”

Wendy and Tom have at times added to their endowments, which continue to grow in value through Yale’s investment office.

“That’s what Tom and I like about endowments in general,” Wendy said. “Once they are established, we can add to them along the way to increase their impact, and they will continue to contribute to the mission forever.”

Wendy and Tom Naratil have established a new endowment, directed toward helping the center meet its annual operating expenses, because, Wendy said, “If you don’t support the day-to-day costs, the center cannot do all the wonderful things it does.”
The Health of Women Faces an Emergency  
By Rick Harrison

In May, a study in the Journal of the American Heart Association reported that women experiencing chest pain in hospital emergency rooms nearly 11 minutes longer than men before they are seen by a health care provider. Women with chest pain were also less likely than men to be admitted to the hospital or kept under observation.

This is true even as heart disease remains the most common killer of women, accounting for more than one in five deaths. The JAH A study also found that people of color with chest pain also waited to be seen by a physician longer than White adults with the same symptoms.

The study is among the latest in a string of reports describing what has become known as “medical gaslighting,” a phenomenon in which people view themselves and reach decisions about their lives. This means studying the particular health needs of women and the effects of sex, gender, race, and ethnicity on health. For nearly 25 years, Women’s Health Research at Yale has led that charge.

For nearly 25 years, WHRY has successfully challenged inequitable traditions in order to guarantee that sex-and-gender differences are studied, learned from, and taken into account when solutions to the health issues women face. They understand the center’s mentorship of new researchers. They learned from, and taken into account when solutions to the health issues women face. They understand the center’s unique and necessary role the center plays in identifying and funding the studies that explore innovative solutions to the health issues women face. They understand the center’s capacity to attract and assemble the world’s leading research and clinical experts, the center’s proven success at forming interdisciplinary research teams, and its informed and compelling voice in advocating for health equity.

Our supporters invest in WHRY’s mentorship of new researchers. They invest in WHRY’s ability to identify the skills and focus needed to expand this work and ensure implementation of new approaches to clinical care. They see the proven value in communicating the results of our research to the medical community and the general public. And, finally, our supporters underwrite WHRY’s partnership with the policy lab Elevate in order to leverage data-driven solutions to benefit women and families living in underserved communities.

To continue this work, every dollar counts. Even as threats to the health of women accelerate, WHRY will continue to outpace them by trusting the science. And by putting our faith in the education of researchers, practitioners, and the public alike.

With my appreciation for your generosity,

Barbara M. Riley  
Philanthropy Chair
Women’s Health Research at Yale

Women’s Health Research at Yale is changing the landscape of medical research and practice by ensuring the study of women and examining health differences between and among women and men to improve the lives of everyone.

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