Ovarian Cancer:
A Silent Killer "Speaks" through Proteins

***Elise Kohn, M.D.**, is passionate about expanding our knowledge of ovarian cancer through teaching. When she is not mentoring the next generation of scientists and physicians, this 22-year veteran of NCI spends her days moving from bench to bedside—literally—as she leads both the Molecular Signaling Section ("bench") and the Medical Ovarian Cancer Team ("bedside") within the Medical Oncology Branch of CCR. And when she is not in the clinic or in the lab, Kohn is on the phone providing consultations for other patients across the country who seek her guidance after learning about her program through the Ovarian Cancer National Alliance, National Ovarian Cancer Coalition, and other ovarian cancer networks. CCR has provided Kohn with unparalleled opportunities to advance her science, which may not have received the same funding and support outside of the intramural program. This has allowed her to break ground in the clinical arena as she and her team find new ways to both diagnose and treat the no longer so-called "silent killer" known as ovarian cancer.*

(*Image: R. Baer*)

Elise Kohn, M.D.

The American Cancer Society estimates that 21,650 women in the United States will be diagnosed with ovarian cancer in 2008; 15,000 will die of their disease. The good news is that women who present with Stage I ovarian cancer have a greater than 90 percent chance of being cured. The bad news is that only 20 percent of patients are diagnosed at this early stage of disease. Less than 35 percent of patients with advanced-stage disease—80 percent of all women diagnosed—will survive beyond five years. This sobering statistic is the reason that ovarian cancer is the leading cause of gynecologic cancer death in the U.S. and why it ties with pancreatic cancer for fourth place in women's overall cancer mortality.

Barriers to Early Detection

Early detection, critical for surviving ovarian cancer, is one of the most imperative issues in ovarian cancer care, but it is most certainly not easy. Due to the elusive nature of the disease, there are a number of reasons why ovarian cancer used to be referred to as the "silent killer."

Ovarian cancer is difficult to detect. The ovaries lie deep within the abdominopelvic cavity, making them difficult to view or feel. It was initially believed that ovarian cancer lacked warning signs, although we now know that there are subtle symptoms that may suggest disease. In 2007, the American Cancer Society, the Gynecologic Cancer Foundation, and the Society of Gynecologic Oncologists released a consensus statement claiming that symptoms often do exist for ovarian cancer, even in the early stages. These symptoms include bloating, feeling full quickly, pelvic or abdominal pain, and frequent or urgent urination.[1] The problem with these symptoms is that they are common and occur with a number of ailments. But, if they occur almost daily and last for more than a few weeks, women should see a gynecologist. It remains to be seen whether this symptom checklist will help women detect ovarian cancer sooner rather than later.

Another hurdle to early detection is the lack of validated screening tools to identify disease. The Papanicolaou ("Pap") test is used to screen for cervical cancer and the mammogram to screen for breast cancer, but there is no validated

and robust test that can identify ovarian cancer. The biomarker CA-125, a protein in the blood that is sometimes elevated in women with ovarian cancer, is approved to monitor response to treatment as well as to detect recurrent ovarian cancer, but it is not sensitive and specific enough to identify early disease or to have an impact on survival. This lack of effective molecular diagnostics is why there is a great need to identify alternative biomarkers that can detect cancer at Stage I—when the disease is most amenable to cure.

CCR's Ovarian Cancer Medical Team is running a number of clinical trials to achieve two critical goals: to test the use of combinations of molecularly targeted therapies to treat recurrent and refractory disease; to identify diagnostic biomarkers for early detection and recurrent disease; and as a companion diagnostic with treatment.

We work from an understanding of the critical role that protein pathways, or networks, play in cancer. We postulated some time ago that future therapeutics will target entire protein networks, not just one protein. For this reason, we have invested our energies into the application of proteomics (the study of proteins and their networks) in both the laboratory and clinic. Blood and/or tissue samples are obtained from all patients for use in analyzing protein networks with the goal of developing life-saving diagnostic tests. This work has allowed the once-silent killer to be heard.

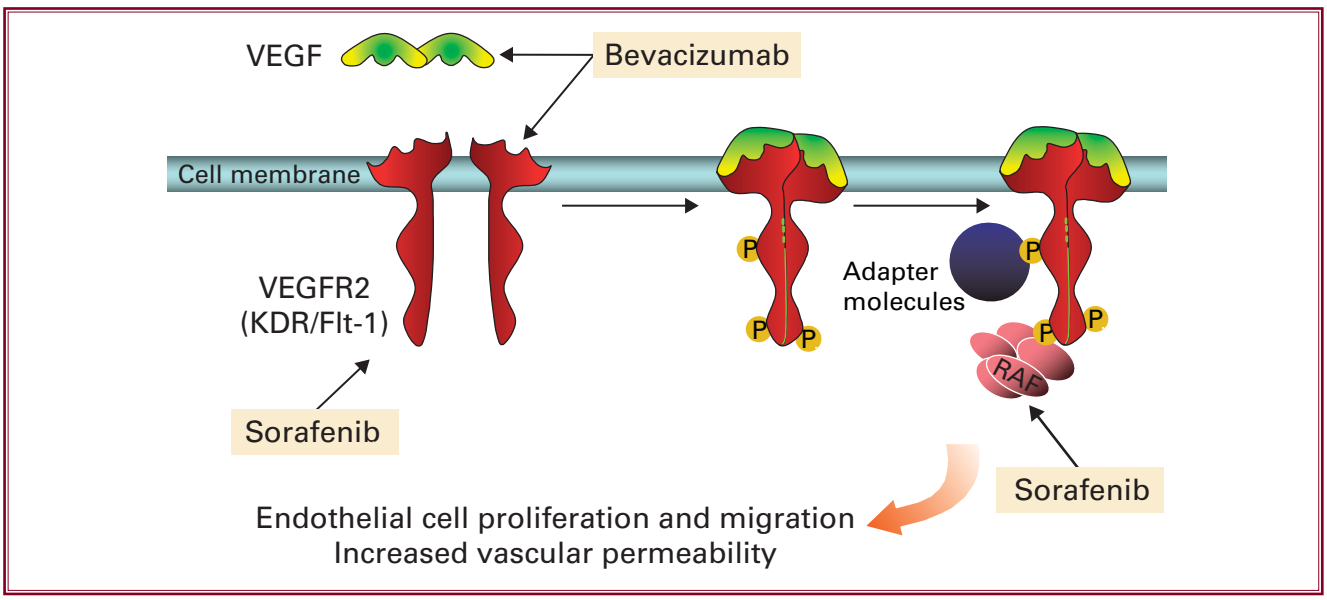
A Mix of Molecularly Targeted Therapies

Ovarian cancer will return in approximately 90 percent of patients who have advanced stage disease. Because recurrent ovarian cancer cannot be cured, it must be treated as a chronic disease, with the understanding that with chronicity comes a need for optimal benefit and minimal risk. We are running early stage clinical trials (Phase I and II) of targeted therapy combinations for recurrent and refractory tumors. These early trials will help determine how a drug might best be given, how often, at what dose and, most importantly, how safe it is in patients. The studies are also designed to address proof of concept, determining whether the drug (or combination) does what it is supposed to do.

Understanding the protein profile of a patient's tumor may help identify treatments that deliver the best outcome for the individual patient. My colleagues and I coined the concept of "personalized molecular medicine" in 2001.[2] If a signaling pathway is overactive in a patient's tumor, targeting that pathway at multiple points simultaneously may more effectively control the activity and at potentially lower doses of both agents.

Targeting the vascular endothelial growth factor (VEGF) pathway, well known to be a critical pathway for the process of angiogenesis is a hypothesis currently being explored in our clinic. Angiogenesis is a normal physiological process that occurs when new blood vessels grow from existing blood vessels. In 1971, the late Judah Folkman, M.D., first proposed that tumors relied on angiogenesis for survival; if they were denied this blood supply, the tumors would die. In 1974, Lance Liotta, M.D., Ph.D., demonstrated that angiogenesis was necessary for metastasis, the process of cancer dissemination. After decades of disregard, angiogenesis became widely accepted throughout the scientific and medical communities, and the field of anti-angiogenesis therapy was born. In the clinical trials being conducted here at CCR, such therapies are used in an attempt to "starve" the ovarian tumors.

My team and I have recently reported on the safety and efficacy of a combination of two agents that block angiogenesis: bevacizumab (Avastin®) and sorafenib (Nexavar®). Although both agents target the VEGF pathway, each does it through different mechanisms (Figure 1). Bevacizumab, FDA-approved for non-small cell lung cancer and metastatic colorectal and breast cancers, is an anti-VEGF monoclonal antibody that prevents VEGF from binding to its receptor (VEGFR). Sorafenib, FDA-approved for advanced renal cell carcinoma and hepatocellular carcinoma, is a small molecule drug that blocks VEGFR2 and downstream signals that are activated by VEGF.



(Image: J. Kelly)

Figure 1: Kohn and colleagues are the first to target the VEGF signaling pathway in series by combining the anti-angiogenesis treatments bevacizumab and sorafenib. Ongoing clinical trials indicate that this approach inhibits the pathway at two different points; as such the combination therapy holds promise for the treatment of refractory or recurrent ovarian cancer.

Our hypothesis is that targeting the VEGF pathway in series rather than in parallel will enhance the effects of both agents. We are also inhibiting the pathway at two different points—in endothelial (blood cells) and epithelial cells (ovarian tumor cells)—using this strategy. Our clinic is the first to target VEGF signaling in series with combination specific anti-angiogenesis therapy.

There are two clinical trials under investigation using this combined treatment. In a Phase I study, 62 patients with refractory, metastatic, or unresectable solid tumors of any type have been enrolled. This study is addressing identification of optimal doses, safety, and toxicity of this regimen in these patient populations. Tumor samples have been obtained from which to measure changes in the targeted protein networks and correlate them to a clinical outcome.

The second study using this combination therapy is a Phase II study specifically for patients with recurrent ovarian, fallopian tube, or primary peritoneal cancers. The objective of this trial is to confirm potential benefit of sorafenib and bevacizumab in these patients and to help guide further application of the regimen outside of NCI. Initial Phase I data in these patient populations showed promising activity in tumors known to have increased VEGF pathway signaling, but with synergistic anti-tumor activity at doses below the standard single agent treatment doses. Thirty-three percent of all treated patients had some reduction in tumor size—some quite rapidly—and many of the rest saw their tumors stabilize (Figure 2). Combination therapy reduced the blood supply to many patients' tumors. We observed a greater benefit than was expected in a Phase I clinical trial, and this has given us hope that these results will be reproduced in the ovarian cancer Phase II study.

We will analyze patient tumor samples, collected prior to treatment and while patients were on therapy, to investigate whether those who had a good response to treatment displayed an initially overactive VEGF pathway or one inhibited by treatment.

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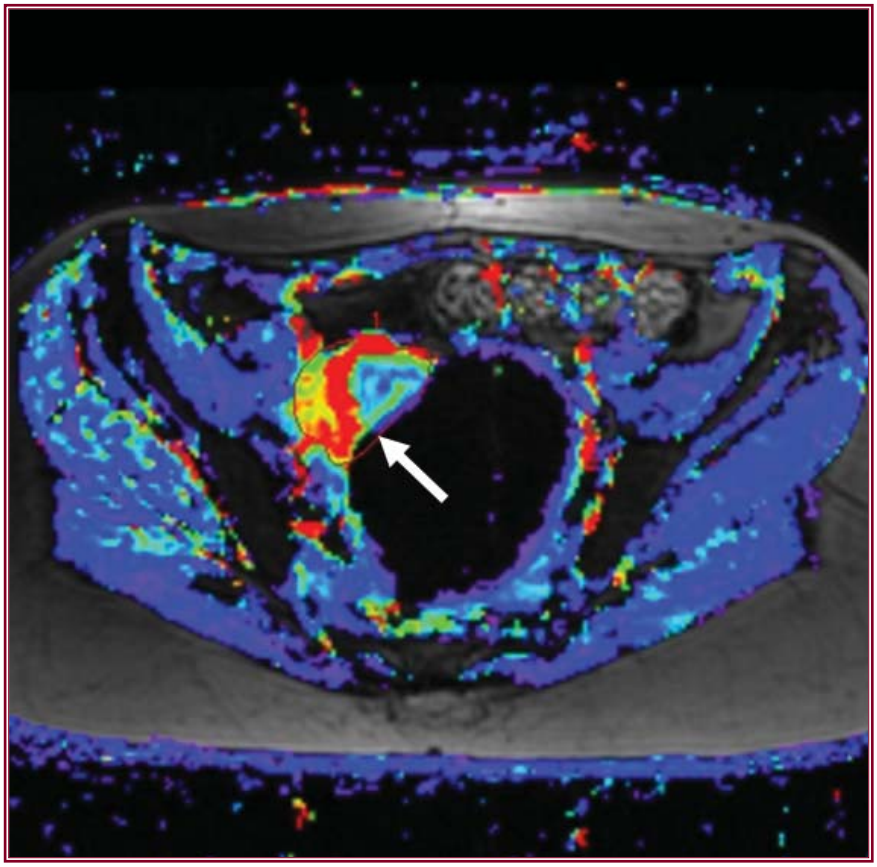

(*Image: P. Choyke, CCR*)

The resulting data could provide further justification for tailoring therapy to a tumor's protein profile and could result in a companion predictive test for this combination therapy, allowing doctors to monitor response during treatment.

Diagnostic Biomarkers

The lack of a validated screening test for ovarian cancer has prompted investigators to seek alternative diagnostic strategies. Tumors leak proteins into body fluids, including blood and urine, and some of these proteins may be able to alert doctors to the presence of disease. These cancer-related proteins are known as cancer biomarkers. By collecting these fluids, it may be possible to develop a biomarker that may diagnose cancer at an early stage.

Biomarker use is not a new concept. Elevated prostate specific antigen (PSA) is an example of a biomarker that can be detected in men who have organ-limited prostate cancer. Technologies for detecting proteins and our understanding of the underlying relationship between proteins and cancer have come a long way. These scientific advancements are being translated to clinical trials to benefit our patients.

My ovarian cancer team and I are in collaborations to analyze blood samples from ovarian cancer patients for protein "signatures," or patterns of proteins, that can predict early-stage ovarian cancer and cancer recurrence. In particular, candidate biomarkers will be compared against or tested alongside the CA-125 biomarker to determine whether they are more effective than this biomarker in predicting ovarian cancer's return.

In order to carry out this biomarker research, my colleagues and I are developing a repository, or bank, of blood samples from patients enrolled in one of the clinical trials. Because few, if any, cancers are characterized by a single reliable biomarker, such as PSA, this sample collection is critical. We will collect and analyze a large number of blood samples. Our trial is designed to accrue samples from 400 women with the goal of identifying signatures and biomarkers that may have true value in predicting ovarian cancer relapse.

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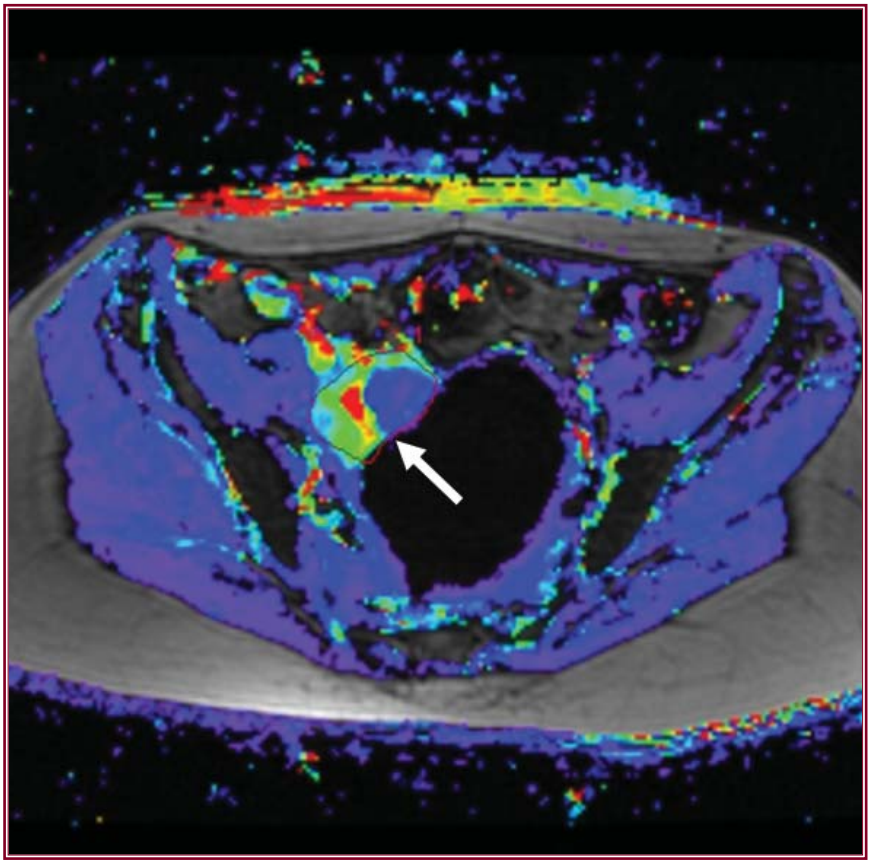
[1] *Goff BA et al. Development of an ovarian cancer symptom index: possibilities for earlier detection. Cancer.* 2007;109(2):221-227. *The full text of this publication is available at http://preview.tinyurl.com/5ox5zq.*

[2] *Liotta LA, Kohn EC, Petricoin EF. Clinical proteomics, personalized molecular medicine. JAMA.* 2001;286(18):2211-2214.

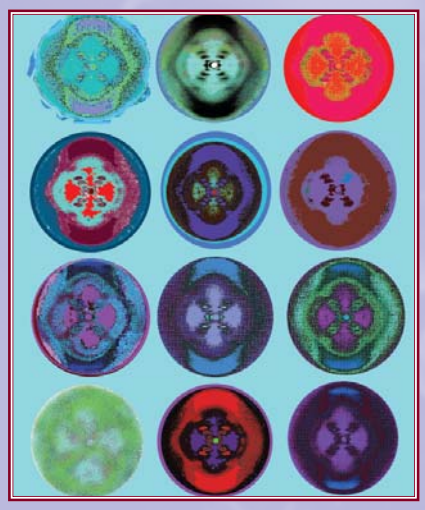
To learn more about Dr. Kohn's work, *visit http://ccr.cancer.gov/staff/staff.asp?profileid=5844*



(*Image: P. Choyke, CCR*)

Figure 2: The difference in a tumor's blood flow before *(left, red and yellow region next to arrow)* and after *(right)* treatment with a combination of anti-angiogenic therapies can be striking. In a Phase II clinical trial, thirty-three percent of patients treated with sorafenib and bevucizumab, which target different components of the angiogenic pathway, saw some reduction in tumor size.

Answering the Voices of Family History



(*Image:* A Vision of Rosalind Franklin *for* OCNA ©2006 Wyllie O Hagan)

"Vision of Rosalind" is an artistic rendition of Rosalind Franklin's pioneering first glimpse of the X-ray crystal structure of DNA, created by an artist and ovarian cancer survivor to honor Franklin's personal battle with the disease that ultimately took her life. The artist and Elise Kohn, M.D., met in 2006, the year Kohn received a Rosalind Franklin Excellence in Ovarian Cancer Research Award from the Ovarian Cancer National Alliance.

Katherine Horn, of Montgomery County, Md., came by her predisposition for cancer "honestly"; she carries a BRCA mutation, a type of genetic mutation that makes her more susceptible to breast and ovarian cancer. Cancer is prevalent throughout her family tree, including a male second cousin who had breast cancer, as well as two out of her three sisters who had previous bouts of breast cancer.

Early in 2005, Horn began noticing symptoms that included abdominal bloating and headed straight to her oncologist. "I knew with my family history that I was in big trouble," said Horn. In May of 2005, Horn's oncologist confirmed the diagnosis of ovarian cancer. Though devastating, the diagnosis did not come as a complete surprise, and though successful, the surgery revealed that the cancer had spread to the lymph nodes.

Horn responded well to treatment with paclitaxel (Taxol®) combined with intraperitoneal cisplatin, a recently recognized advance in the treatment of ovarian cancer, but in April 2006 a blood test revealed that her CA-125 (a protein biomarker associated with ovarian cancer recurrence and response to treatment) had gone up again. "I really wanted to go after it aggressively," Horn said, and she began another round of treatment.

Unfortunately, Horn's CA-125 levels started to climb again soon after her second treatment regimen ended. She went through this experience several times. Then her doctor, benefiting from a resident NIH nurse in his office who helps link patients with clinical trials at CCR, suggested that she join a clinical trial being run by Elise Kohn, M.D.

Though Horn met all of the trial criteria and began treatment in January 2008, an adverse reaction forced her to withdraw from the study. However, her positive experience at CCR and with the community of doctors and nurses there has led her to seek treatment in another clinical trial being run by Kohn, this one designed specifically for patients with the BRCA genetic mutation.

When speaking of Kohn, Horn emphasized the unique and supportive relationship that Kohn and the entire CCR staff strive to maintain with their patients. "It's that extra supportive layer," explained Horn. "My relationship with Dr. Kohn is not just a doctor-patient relationship. I know something about her life outside of CCR, and she knows something of mine.

"Not only are the doctors, nurses, and hospital staff wonderful," Horn continued, "but the physical facility itself is the most relaxing, comfortable hospital I've ever been in. As a former project manager for hospital renovations," she said, "I should know; I used to work in them!

I would definitely encourage people to try CCR," Horn said. "You're getting really avant garde medical treatment, and you're getting absolutely fantastic emotional and medical treatment from the staff."

Sharon Morris also understands the impact that a family history of cancer can have on both the past and the present. In her family, cancer is considered the "family curse." "I watched my father, my grandfather, my cousins, so many people in my family, die young," said Morris. Morris has the BRCA1 mutation. This mutation, a part of her family tree for generations, would come to affect her as well.

After taking time off to care for her mother, Morris, a former banker from New Jersey, was inspired to go back to school to become a certified surgical technician. Just after her graduation in December 2007, she began to notice unusual abdominal swelling, despite a good report following a gynecological exam the month before. Morris sought the advice of the obstetrician who helped deliver her two daughters. She was diagnosed with ovarian cancer by January 2008 and started treatment at the Robert Wood Johnson University Hospital in New Brunswick, N.J.

After two courses of standard treatment and surgery, Morris entered remission, but the cancer returned two months after she finished her second round of treatment. It was then that her oncologist suggested that conventional treatment might not be the answer for her, and she started looking into clinical trials. Unfortunately for Morris, she had an adverse reaction to the treatment in her first clinical trial and did not have positive results with the second. Morris started researching other possibilities for treatment. "From the day I was diagnosed," said Morris, "I would research, 24/7. If you could have a master's degree in ovarian cancer, I would have it."

Morris read about a new type of cancer treatment, the poly (ADP-ribose) polymerase inhibitor (PARP inhibitor). This type of drug has shown to be an exciting and promising advance for women with the BRCA1 and BRCA2 mutations, with the added benefit of fewer toxic side effects than standard chemotherapy treatments. Her interest in PARP inhibitors and a suggestion by her doctor led her to CCR, and she has enrolled in a PARP inhibitor-focused clinical trial being conducted by Kohn.

Though Morris only started her treatment with Kohn in June, her experience with CCR has been nothing but positive. "I have never gone to a place like CCR," explained Morris. "People at the NIH are in a class by themselves."

Given Morris's family history with cancer, she realizes that her participation in research at CCR is not just for her but for her entire family. "Everyone who has been afflicted with the BRCA1 mutation is gone," stated Morris. "But it ends here."

Morris is hopeful about her trial with Kohn and believes that the same feeling of hope can be found throughout the entire CCR community. "CCR doesn't talk about recurrence, progression, or survival statistics," explained Morris. "But when you do go to CCR, you *will* hear, 'Let's all hope together.'"