CDMRP

V. Ovarian Cancer Research Program

THINKING DIFFERENTLY

Vision

To eliminate ovarian cancer.

Mission

To support research to detect, diagnose, prevent, and control ovarian cancer.

The Disease

Ovarian cancer ranks second among gynecological cancers in the number of new cases and first among gynecological cancers in the number of deaths each year.

- It is estimated that in 2007, approximately 22,430 women will be diagnosed with ovarian cancer in the United States.
- An estimated 15,280 women will die from ovarian cancer this year.
- Overall, the 5-year survival rate for all stages of ovarian cancer is approximately 45 percent. However, local ovarian cancer has a 93 percent 5-year relative survival rate, thus emphasizing the need for early diagnosis.[1]

OCRP Making Headlines

- **MIT Works Toward Safer Gene Therapy, Biodegradable Polymers Replace Viruses to Deliver Genes**
  MIT News, September 7, 2007
- **Study Pries into Ovarian Cancer's Deadly Secrets**
  University of Michigan Health System News, April 11, 2007

[1] American Cancer Society – *Cancer Facts and Figures*, 2007.

Signs and Symptoms

The Gynecologic Cancer Foundation, the Society of Gynecologic Oncologists, and the American Cancer Society led the effort to develop a landmark consensus statement on ovarian cancer symptoms. This statement was released in June 2007 and was endorsed by over 15 organizations including the Ovarian Cancer National Alliance.

The following symptoms are much more likely to occur in women with ovarian cancer than women in the general population:

- Bloating
- Pelvic or abdominal pain
- Difficulty eating or feeling full quickly
- Urinary symptoms (urgency or frequency)

Women with ovarian cancer report that symptoms are persistent and represent a change from normal for their bodies. The frequency and/or number of such symptoms are key factors in the diagnosis of ovarian cancer. Several studies show that even early-stage ovarian cancer can produce these symptoms. Women who have these symptoms almost daily for more than a few weeks should see their doctor, preferably a gynecologist. Prompt medical evaluation may lead to detection at the earliest possible stage of the disease. Early-stage diagnosis is associated with an improved prognosis.

While these nonspecific symptoms are not always related to a serious condition, many women with ovarian cancer recall experiencing these symptoms.

Program Background

During the 1990s, ovarian cancer advocates launched a grassroots campaign to increase federal funding for ovarian cancer research. In response to these efforts and increased public awareness for additional research, in fiscal year 1997 (FY97) Congressional Appropriations Conference Committee Report No. 104-863 provided $7.5M for peer-reviewed ovarian cancer research, marking the establishment of the Department of Defense (DOD) Ovarian Cancer Research Program (OCRP). Congress continued to appropriate targeted funds to the DOD OCRP, totaling $111.7M from FY97 to FY07 (see Figure V-1, OCRP Funding History). Since its inception, the OCRP has been thinking differently about how to drive scientific progress in ovarian cancer. Whether building critical research resources, supporting innovative research, or bringing talented investigators into the ovarian cancer field, the program is recognized as a major leader in extramural ovarian cancer research. A total of 130 awards have been made through FY06 across research, training and recruitment, and research resources.

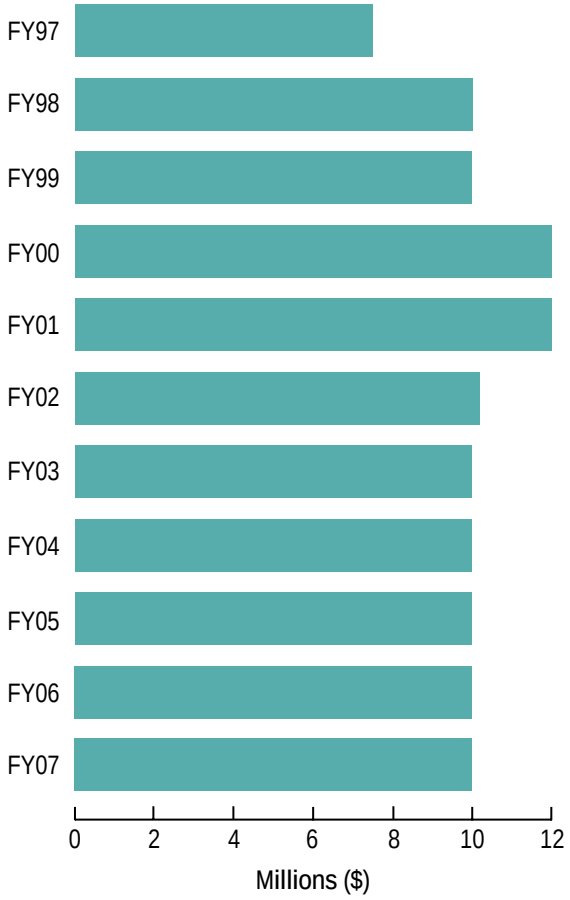
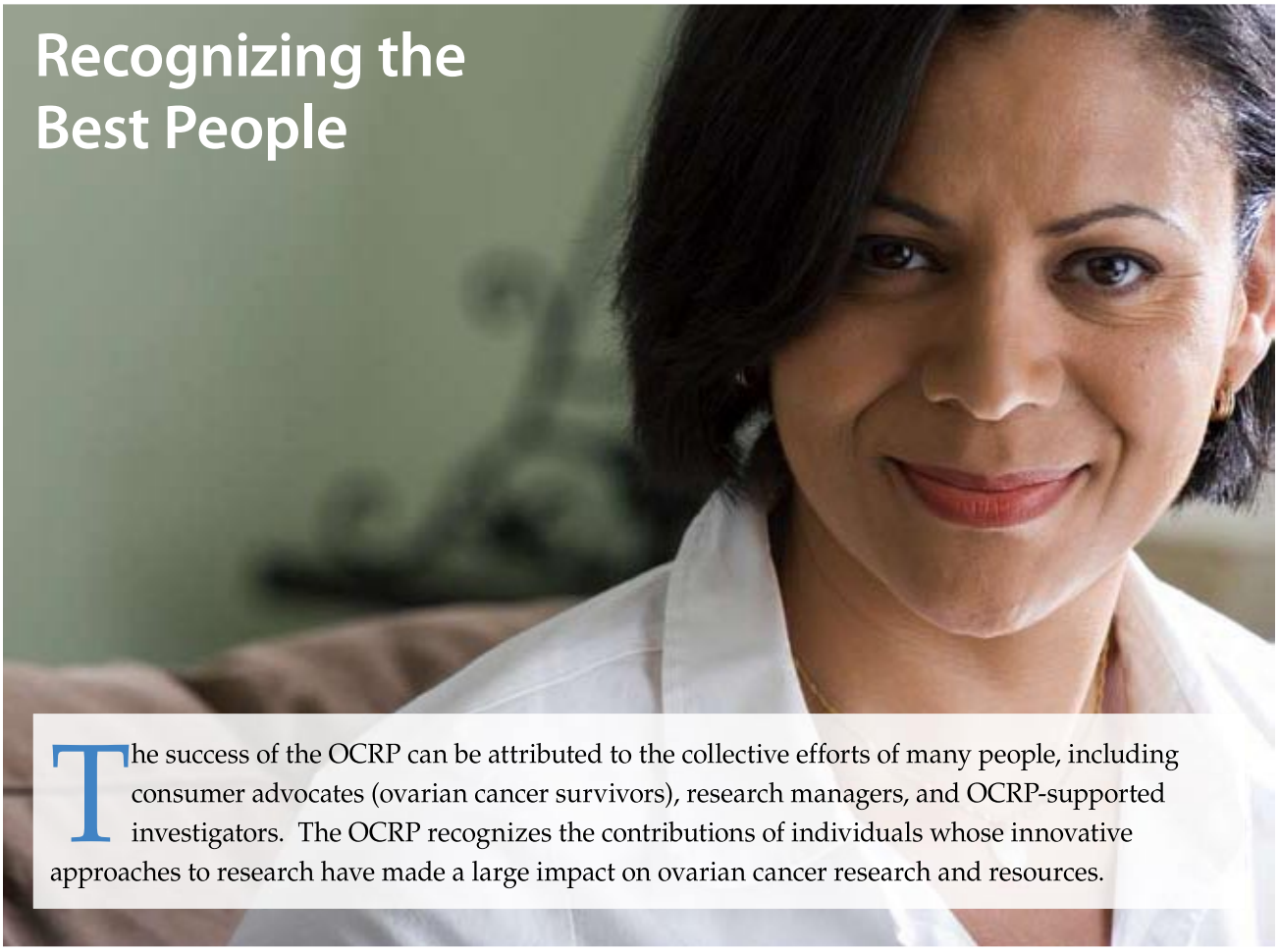


Figure V-1. OCRP Funding History



Recognizing the Best People

The success of the OCRP can be attributed to the collective efforts of many people, including consumer advocates (ovarian cancer survivors), research managers, and OCRP-supported investigators. The OCRP recognizes the contributions of individuals whose innovative approaches to research have made a large impact on ovarian cancer research and resources.

Consumer Advocates

Following the FY97 appropriation, consumer advocates participated in the DOD OCRP stakeholders meeting held in April 1997 to provide input for the new program. Consumers were thinking about ovarian cancer research from a different perspective—they wanted to ensure that the program developed award mechanisms and funded awards that filled current gaps in ovarian cancer research. From that point forward, consumer advocate participation has remained a critical component of the success of the OCRP. As active members of the OCRP, consumer advocates participate in the peer review of proposals as well as in setting program priorities and making funding recommendations. Approximately **75 consumer advocates** have contributed to these processes since 1997. Consumer advocates' firsthand experiences with ovarian cancer provide a unique perspective that is complementary to the expertise of the scientists and clinicians on the panels. Moreover, this perspective helps scientists understand the human side of how research will impact the community and allows for funding decisions that reflect the concerns and needs of patients, the clinicians who treat them, and survivors and their families. Equally important, consumer advocates take what they have learned from the scientists back to their advocacy communities. This results in increased awareness of the importance of research and a stronger relationship between the scientific and consumer advocate communities. Additional information about consumer advocate participation can be found in Section I, Overview.

Marianne Mills
Responsible Ovarian Awareness Required!
FY06–07 Consumer Peer Review Panel Member

"Being a mentor to a novice consumer reviewer is similar in some ways to providing support to a newly diagnosed woman. Both are new experiences that bring questions and moments of doubt and anxiety. However, the novice reviewer has moved beyond her disease to become an advocate for others in a very powerful way, and it is an honor to be able to support that transition."

Peer Review Panel Members

OCRP peer review panel members represent a prominent group of research scientists, clinicians, and consumer advocates from the ovarian cancer field. Peer review panel members provide unbiased, expert advice on the scientific and technical merit of proposals submitted to the program. Scientific reviewers are selected for their subject matter expertise and experience with scientific peer review. Consumer reviewers are nominated by an advocacy or support organization and are chosen on the basis of their leadership skills, commitment to advocacy, support, and outreach as well as their interest in expanding their scientific knowledge. Nearly **500 clinicians, scientists, and consumer advocates** have contributed their expertise to peer review for the OCRP. Further details about the peer review process can be found in Section I, Overview.

Integration Panel Members

The OCRP Integration Panel (IP) is composed of eminent research scientists, clinicians, and consumer advocates who are all leaders in their respective communities. Members of the IP refine the program focus and investment strategy and recommend a broad portfolio of proposals for funding that reflects the investment strategy for that particular program cycle (for more information about the advisory functions of the IP, see Section I). Thus, the recommendations of individual IP members help enable the OCRP to find and fund cutting-edge research and set important program priorities aimed at eliminating ovarian cancer.

FY07 OCRP IP Members

Nita J. Maihle, Ph.D. (Chair), Yale University School of Medicine

Jeffrey Boyd, Ph.D. (Chair Emeritus), Anderson Cancer Institutes

James P. Basilion, Ph.D., Case Western Reserve University

Lora Hedrick Ellenson, M.D., Weill Medical College of Cornell University

Patricia Goldman, Ovarian Cancer National Alliance

Thomas Hamilton, Ph.D., Fox Chase Cancer Center

Elise Kohn, M.D., National Cancer Institute

Nyrvah Richard, In My Sister's Care

Stephen Rubin, M.D., The University of Pennsylvania Medical Center

Nicole Urban, Sc.D., Fred Hutchinson Cancer Research Center

Michael Van Seiden, M.D., Ph.D., Massachusetts General Hospital

S. Diane Yamada, M.D., University of Chicago Hospitals

Nita J. Maihle, Ph.D.
Yale University School of Medicine
FY07 Integration Panel Chair

"Over the past year, cancer researchers and oncologists have made strong advances in our collective fight against ovarian cancer, both on the research front and in moving new discoveries into the clinic. Specifically, the synergistic efforts of physicians, scientists, and patient advocates have resulted in early-stage success for several new, biologically targeted therapeutics and also in the development of promising new biomarkers for the early detection of ovarian cancer. These unprecedented developments are, in large part, the result of funding targeted to the nation's ovarian cancer research efforts by the DOD's Ovarian Cancer Research Program. This funding also has been used to pioneer several new directions, as well as to enhance the critical infrastructure necessary to support continued breakthroughs in this field."

The Scientif c Community

The OCRP has supported over **184 exceptional scientists and clinicians** who are committed to impacting the field of ovarian cancer and have demonstrated that thinking differently is important. Whether working individually or together, OCRP investigators demonstrate that they are asking research questions and proposing studies that focus on the needs of the consumer community.

Denise C. Connolly, Ph.D.
Fox Chase Cancer Center
FY03 New Investigator Award Recipient
FY06 Concept Award Recipient

"I have been the fortunate recipient of two Ovarian Cancer Research Program awards. These awards came at a critical period when starting a new lab and provided the much-needed resources to initiate projects that had limited preliminary data and were somewhat risky. Receiving these awards enhanced my own confidence in my program and provided valuable recognition by my scientific colleagues. I am very grateful to the OCRP for these opportunities."

Thinking Differently

Thinking Differently about Early Detection

Q. I was recently diagnosed with stage III and grade III ovarian cancer. I have yearly checkups and have always been fine. I had no noticeable symptoms, except some increased urinary frequency in the past few months. How could this have happened and how could my cancer have been caught earlier?

A. Ovarian cancer presents a challenge for early detection. Because of the anatomy and location of the ovaries, cancer cells can shed off the outer surface of the ovaries and fairly easily implant in the abdominal cavity because of limited tissue barriers. Many investigators believe that ovarian cancer has much shorter stage I and stage II times as compared to other cancers.

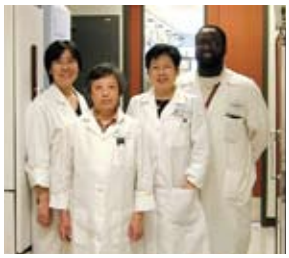
Despite these challenges, many investigators believe that improved early detection of ovarian cancer is possible. The Ovarian Cancer National Alliance and 20 other cancer organizations recently published an ovarian cancer symptoms consensus statement. They found that ovarian cancer is not a "silent killer," and the following symptoms are much more likely to occur in women with ovarian cancer than women in the general population: bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, and urinary symptoms (urgency or frequency).

Noureddine Melikechi, Dr. Phil.
Delaware State University
FY05 HBCU/MI Collaborative Research Award Recipient

"All I am learning about ovarian cancer is made possible by the Ovarian Cancer Research Program. Shining new light on this deadly disease is not only fascinating but also informative."

Many investigators are attempting to develop new tests for early detection of ovarian cancer, especially blood-based biomarker tests and new imaging tests. Currently, the CA-125 test is used in high-risk populations. Although CA-125 is a good biomarker, it lacks sufficient specificity and sensitivity to be used as a screening tool in the general population. Ultrasound detection also lacks sufficient specificity and sensitivity for use in the general population.

OCRP investigators are thinking differently about early detection and using new and innovative approaches to developing new biomarker and imaging tests.



Gordon Mills', M.D., Ph.D., research team
University of Texas M.D. Anderson Cancer Center

Using a "Theragnostics" Approach to Early Detection

Dr. Gordon Mills of the University of Texas M.D. Anderson Cancer Center is using an innovative theragnostics approach for the early detection of ovarian cancer. Theragnostics is the association of a diagnostic test with a therapy. With funding from an **FY02 Idea Development Award**, Dr. Mills and his team are attempting to detect serum lysophosphatidic acids (LPA) by using two technologies: the development of antibodies that will recognize specific phospholipids and lysophospholipids present in ovarian cancer patients, and affinity binding and surface enhanced laser desorption/ionization time of flight mass spectrometry. These two technologies will then be combined with powerful computing tools to develop algorithms for the detection of ovarian cancer at an early, curable stage.

Dr. Mills and his team developed LPA antibodies and tested their diagnostic and therapeutic abilities. They also expanded their approach to involve other targets in LPA pathways. They developed antibodies against the related bioreactive lysophospholipid sphingosine-1 phosphate, developed LPA analogs, and developed carba analogs of cyclic phosphatidic acid (these are selective inhibitors of autotaxin, the enzyme that produces LPA). All of these approaches showed promising results in cell models as potential new theragnostics for ovarian cancer.

Zhen Zhang, Ph.D.
Johns Hopkins University

New Multicenter Approaches to Biomarker Discovery

Dr. Zhen Zhang of Johns Hopkins University is discovering and validating new serum biomarkers for early detection of ovarian cancer through a multicenter approach. With funding from an **FY03 Idea Development Award**, Dr. Zhang is using multiple data sets from samples collected at independent and diverse sites to reduce false-positive results that commonly occur in biomarker studies due to non-disease-related biases in data.

Dr. Zhang's research team showed that specific patterns of fragments of human serum inter-alpha-trypsin inhibitor heavy chain 4 correlated with the presence of ovarian cancer, as well as other cancers including breast, colon, prostate, and pancreatic, as well as with diabetes.

Dr. Zhang has also applied for patents on two additional candidate biomarkers (hepcidin and CTAP3) and licensed them to a company. The next step is to validate all three of these biomarkers in clinical trials and determine the best combination of these biomarkers and the standard CA-125 biomarker.

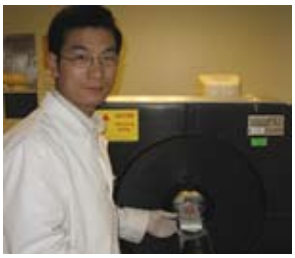
Dr. Noureddine Melikechi, Dr. Phil.
Delaware State University

Using Optical Physics to Identify Elements That Function as Biomarkers

Dr. Noureddine Melikechi of Delaware State University is using sensitive optical spectroscopic techniques to identify new blood biomarkers for early detection of ovarian cancer. With funding from an **FY05 Historically Black Colleges/ Universities and Minority Institutions (HBCU/ MI) Collaborative Research Award**, Dr. Melikechi and his research team are using four different cutting-edge laser optical techniques: laser-induced breakdown spectroscopy, Fourier transform infrared spectroscopy, absorption spectroscopy, and photo-thermal lens spectroscopy.

Dr. Melikechi's team is using these four cutting-edge laser optical techniques to break down blood samples into their elemental composition (e.g., sodium, potassium, and calcium) and to measure absorption spectra of the samples. The team analyzed blood samples from a mouse model of ovarian cancer provided by a collaborator, Dr. Denise Connolly, at Fox Chase Cancer Center. The researchers found exciting preliminary results in which several differences in the spectra were observed between wild-type mice and those with tumors.

This award has also been instrumental in building ovarian cancer research at Delaware State University. Dr. Melikechi has trained four undergraduate and two graduate students under this award. All of the students have presented their work at scientific meetings.



Xiaoyuan Chen, Ph.D.
Stanford University

Using a New Imaging Approach for Early Detection of Ovarian Cancer

Dr. Xiaoyuan Chen of Stanford University is using an imaging approach for early detection of ovarian cancer. This is a unique approach because most early detection approaches are blood based.

Dr. Chen's research team is applying PET (position emission tomography) imaging for noninvasive visualization and quantification of ovarian cancer integrin expression in vivo. These are the first such experiments in this field. Dr. Chen's group focused on targeting $\alpha v\beta 3$ integrin because high levels of $\alpha v\beta 3$ integrin are expressed in primary ovarian cancers, and even higher levels of $\alpha v\beta 3$ integrin are found in malignant ovarian cancers than in those with low malignant potential. Furthermore, $\alpha v\beta 3$ integrin plays a key role in angiogenesis, and ovarian cancer is angiogenesis dependent.

Dr. Chen's team developed peptide tracers that specifically target $\alpha v\beta 3$ integrin and can be used for PET imaging. The researchers developed ovarian cancer model systems and are currently testing the tracers in these systems. This project could lead to new molecular-based methods for improved early detection of ovarian cancer and to new therapies, such as radiotherapy with radiolabeled RGD peptides and chemotherapy with cytotoxic RGD peptide analogues.

Thinking Differently about Treatment of Recurrent Disease

Q. I am an ovarian cancer patient. My tumor was stage III and grade III. I was treated with a combination of carboplatin and taxol. Although my tumor responded well initially, I now have recurrent disease. What are my options?

A. Most ovarian cancer patients, approximately 80 percent, respond well to the standard carboplatin and taxol treatment. However, over half of these women will face subsequent recurrent disease. Consequently, most of the current clinical trials focus on new treatments for recurrent, not primary, disease. Many of the clinical trials are listed on the National Institutes of Health website (http://www.clinicaltrials.gov) and the Ovarian Cancer National Alliance website (http://www.ovariancancer.org/).

Because many of the clinical trials focus on new combinations of existing drugs, OCRP investigators are thinking differently by developing new types of treatments.

New Approaches to Gene Therapy

Dr. David Curiel of the University of Alabama at Birmingham is developing new gene therapy strategies for treating ovarian cancer. With funding from an **FY04 Idea Development Award**, Dr. Curiel's team is using a highly novel "double targeting" approach. This strategy is based upon restricting the expression of the anti-cancer gene exclusively to ovarian cancer tumor cells ("transcriptional targeting") plus directing the binding of the viral vector particle exclusively to tumor cells ("transductional targeting").

Dr. Curiel's group optimized the adenovirus-based system. The researchers found that the novel conditionally replicating adenovirus combined with cisplatin enhanced antitumor efficacy on ovarian cancer in cell and animal models.

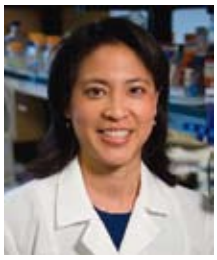
Patricia Goldman
Ovarian Cancer National Alliance
FY07 Integration Panel Member

"The OCRP…has been an incubator for important research that has been, and continues to be, a major factor leading to discoveries to improve diagnosis of and treatment for ovarian cancer."

New Approaches to Overcoming Drug Resistance

Many recurrent ovarian cancers show resistance to platinum drugs, such as carboplatin and cisplatin. Dr. Stephen Howell of the University of California, San Diego, is discovering how ovarian cancer cells develop resistance. Specifically, Dr. Howell's team is studying copper transporters with funding from an **FY02 Idea Development Award**. Dr. Howell's group is focusing on the role of the copper uptake protein CTR1 in mediating transport and sensitivity to the platinum drugs. Dr. Howell hypothesized that CTR1 is the major influx transporter for the platinum drugs and that defects in CTR1 function contribute to impaired uptake of platinum drugs in resistant ovarian tumors. Dr. Howell's team is discovering the mechanisms by which CTR1 controls the cellular pharmacology of the clinically used platinum-containing drugs.

The researchers found that exposure of human ovarian carcinoma cells to cisplatin at clinical relevant concentrations triggered very rapid and extensive loss of hCTR1 expression. The mechanism involved degradation in the proteasome, indicating that proteasome inhibitors and platinum drugs may be an effective combination therapy for recurrent ovarian cancer.



Rebecca Liu, M.D.
University of Michigan

Treating Recurrent Disease by Inhibiting Glucose Metabolism

Dr. Rebecca Liu of the University of Michigan is addressing the problem of chemoresistant disease by using natural compounds to inhibit glucose metabolism. With funding from an **FY05 Idea Development Award**, Dr. Liu's research team is studying resveratrol, a plant compound that is found in peanuts, grapes, and other plants. Resveratrol has antibacterial and antifungal properties and is naturally produced by plants as a defense against infection. Recently, resveratrol was shown to act as a caloric restriction mimetic in yeast, fruit flies, worms, fish, and mice. Dr. Liu's hypothesis was that resveratrol could inhibit glucose metabolism in ovarian cancer cells, thereby promoting autophagy. Autophagy is a distinct form of cell death, normally induced under nutrient deprivation conditions.

Dr. Liu's team showed that resveratrol inhibited glucose uptake in ovarian cancer cell lines. Resveratrol and glucose deprivation preferentially inhibited the growth of ovarian cancer cells. The researchers studied the mechanisms of resveratrol action and found that resveratrol inhibited AKT/mTOR signaling. Interestingly, Glut1 and phosphorylated mTOR were expressed at high levels in ovarian cancer tissue samples from patients. Conventional chemotherapeutic agents such as cisplatin induce apoptotic cell death. Because resveratrol induces cell death through a mechanism distinct from apoptosis, resveratrol treatment may provide a therapeutic advantage in the management of chemoresistant ovarian cancer.

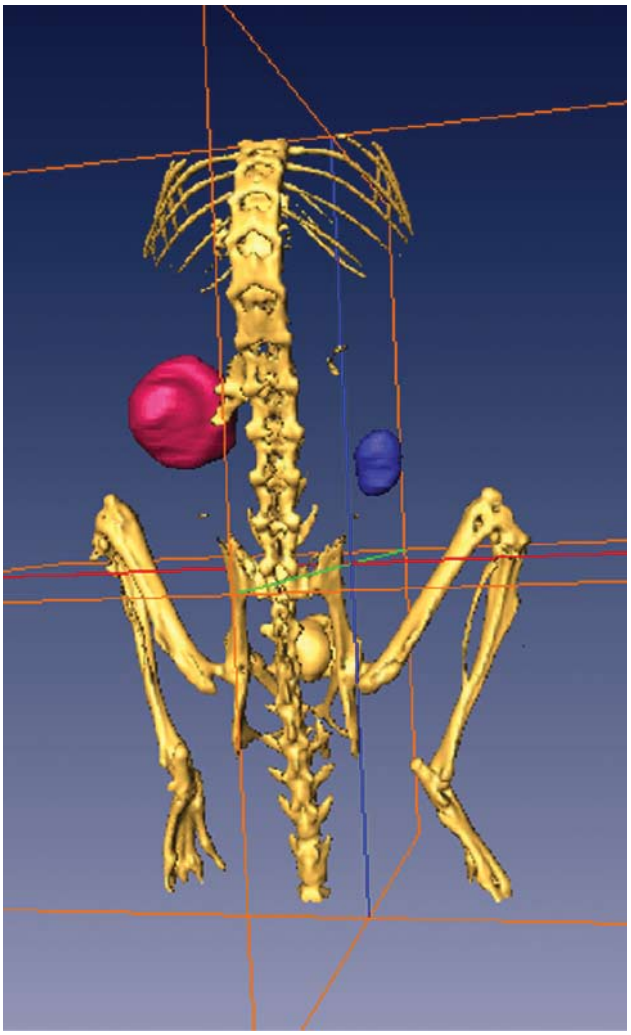
Janet Sawicki, Ph.D., (middle) and her research team Lankenau Institute for Medical Research

Using Nanotechnology and Diphtheria Toxin to Treat Recurrent Ovarian Cancer

Dr. Janet Sawicki of the Lankenau Institute for Medical Research is developing a locally administered gene therapy for advanced-stage metastatic ovarian cancer that would effectively manage the cancer.

Dr. Sawicki's team is using a nanoparticle delivery system that specifically targets ovarian cancer cells. This system would deliver the gene encoding diphtheria toxin, which would act as a suicide gene in the targeted cells.

Dr. Sawicki's team found that direct injection of the diphtheria toxin nanoparticles into ovarian xenografts in nude mice slowed the rate at which tumors grew and the size of the tumors. Furthermore, intraperitoneal administration of the nanoparticles significantly prolonged the lives of transgenic mice bearing ovarian tumors. These results suggest that this novel nanotherapy could be an effective new strategy for treating recurrent ovarian cancer.



Reconstructed CAT scan of a mouse that has two ovarian tumors.

Thinking Differently about Quality of Life

Q. My friend has undergone several treatments for recurrent ovarian cancer. We are all encouraged because the different treatments have been successful, and her disease is being managed almost like a chronic disease. However, she has had many side effects from the medicines. What can she do to improve her quality of life?

A. Quality of life is an important issue for ovarian cancer patients. As management of recurrent disease has improved, ovarian cancer survival rates have increased, but patients undergo a variety of treatments. Therefore, these patients are living with more side effects over longer time periods.

Quality of life is also an important issue for women at high risk for developing ovarian cancer, as this knowledge can create anxiety and indecision about preventive measures.

OCRP investigators are thinking differently about quality of life issues and exploring unique types of interventions.

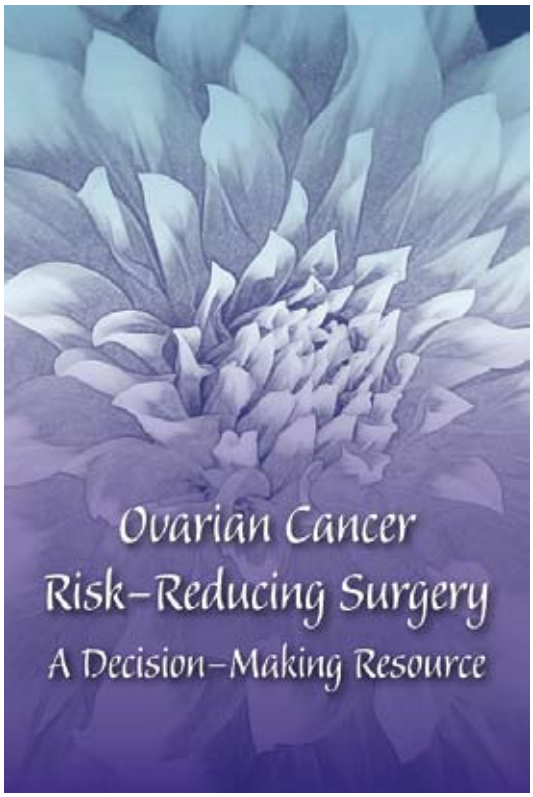
Mary Daly, M.D., Ph.D.
Fox Chase Cancer Center

Quality of Life after Prophylactic Oophorectomy

Dr. Mary Daly of Fox Chase Cancer Center is studying quality of life issues in women who considered undergoing prophylactic oophorectomy, or surgical removal of the ovaries. Many women at high risk for ovarian cancer undergo this surgery as a preventive measure. With funding from an **FY99 Idea Award**, Dr. Daly's team compared two groups: one that proceeded with surgery and another that did not.

Dr. Daly's team showed statistically significant short-term differences between groups with the surgery group experiencing more hot flashes, night sweats, cold sweats, decrease in physical and social functioning, and decrease in sexual activity frequency and pleasure. This was due to the abrupt drop in hormone levels after ovary removal, particularly in premenopausal women. Managing these menopausal symptoms is an important area of clinical intervention. However, despite these short-term menopausal symptoms, women in the surgery group reported an extremely high level of satisfaction and confidence in their decision.

Dr. Daly published the first resource book in the United States designed to present all the information women need as they consider prophylactic oophorectomy for ovarian cancer prevention. This book, "Ovarian Cancer Risk-Reducing Surgery: A Decision-Making Resource," is available to the public at no cost.



Nancy Avis, Ph.D.
Wake Forest University

Identifying Quality of Life Issues at Various Treatment Stages

Dr. Nancy Avis of Wake Forest University received funding to study quality of life among women with ovarian cancer. The primary objective is to identify issues of greatest concern to women in the three treatment stages: newly diagnosed with ovarian cancer, in treatment, and post-treatment. Questionnaires were administered to participants following diagnosis and prior to chemotherapy, during chemotherapy, following chemotherapy, and after recurrence. The secondary objective of the study is to assess changes in quality of life (as determined by the questionnaire) across the different stages of care. This information will be used to target specific interventions to the appropriate treatment stage.

Kathryn Kash, Ph.D.
Thomas Jefferson University

Determining Levels of Distress in Women with a Family History of Ovarian Cancer

Dr. Kathyrn Kash of Thomas Jefferson University is determining levels of distress in women with a family history of ovarian cancer and identifying the mediating factors between risk of developing ovarian cancer and distress. Analysis of study results will be directed toward developing a means to improve the emotional adjustment of women at high risk for ovarian cancer.

Psychological Intervention of Journal Writing to Improve Quality of Life

Dr. Sandra Zakowski of the Rosalind Franklin University of Medicine and Science is attempting to improve the quality of life for ovarian cancer patients and their partners through emotional expression in journal writings. Test subjects in the intervention group were asked to write about their deepest thoughts and feelings regarding their cancer experience for 20 minutes each day for 3 consecutive days. In contrast, the control group was asked to write about trivial nonemotional topics. Follow-up assessments were performed at 1 week, 3, 6, and 9 months post-intervention.

Dr. Zakowski's research team has promising preliminary results that indicate that patients benefited from this intervention. Patients with a low score for the trait of neuroticism showed the greatest benefit. These results suggest that journal writing may be beneficial to quality of life for ovarian cancer patients.

Thinking Differently about Risk and Prevention

Q. My sister and my aunt had ovarian cancer. What is my risk for ovarian cancer? And can I do anything to prevent developing ovarian cancer?

A. Ovarian cancer risk is an important issue, as some families have an inherited high risk for developing ovarian cancer. Alterations in the BRCA1, BRCA2, and HNPCC family of genes are known to confer this risk; other genes are yet to be discovered. Environmental factors may also contribute to ovarian cancer risk. Prevention of ovarian cancer is an important topic to many women but especially to those women at high risk of developing ovarian cancer.

OCRP investigators are thinking differently about risk and prevention by using innovative approaches to determining risk and using new strategies for prevention.

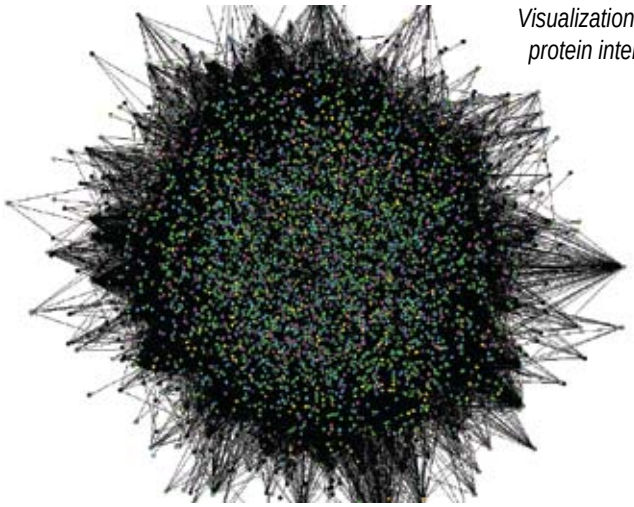
Igor Jurisica, Ph.D.
University Health Network, Toronto
FY04 New Investigator Award Recipient

"OCRP awards provide excellent support for both new and established researchers. The New Investigator Award enabled us to make significant progress on integrative analysis of multiple data sets and multiple types of data on ovarian cancer. During that process we have developed several new tools and resources, which we made publicly available. The two most significant tools include the Interologous Interaction Database and Network Analysis and Visualization software tool to store, analyze, and visualize protein–protein interactions, which enables us to better interpret molecular profiles of cancer. Importantly, while the funding enabled us to make substantial progress toward discovering early diagnostic markers in ovarian cancer, the tools and resources developed are making an impact in other cancers as well, such as breast, prostate, and lung." For more information about Dr. Jurisica's accomplishments, read the research highlight on page V-20.

Using Novel Computational Biology Technologies to Identify Biomarkers That Predict Ovarian Cancer Survival and Risk of Disease Progression

Dr. Jurisica of the University Health Network, Toronto, developed novel computational biology tools. OPHID (Online Predicted Human Interactive Database) is a repository-based system for analyzing existing and emerging data sets on altered gene and protein expression patterns in ovarian and other cancers. OPHID incorporates data from over 16 million published articles and databases, making it several thousandfold larger than any other single existing database. A companion system, NAViGaTor (Network Analysis, Visualization, and Graphing system) was developed by these researchers to create visual renderings of the interactions. These tools are available to the public at no cost.

Dr. Jurisica and his team compared gene expression patterns in patient samples and found 17 genes that were differentially regulated by androgens (hormones associated with prostate cancer) in ovarian cancer cells as compared to controls. Two of these genes, basic leucine zipper transcription factor 2 (BACH2) and acetylcholinesterase (AChE), were upregulated by androgen in ovarian surface epithelial cells derived from women with germline BRCA1 or BRCA2 mutations who underwent prophylactic oophorectomy. Dr. Jurisica's group further investigated BACH2 and AChE using an ovarian cancer tissue microarray from a separate set of 149 clinical samples. Both cytoplasmic AChE and BACH2 levels were significantly increased in ovarian cancer relative to benign cases. High levels of cytoplasmic AChE staining correlated with decreased survival, whereas nuclear localization of BACH2 correlated with decreased time to disease recurrence.

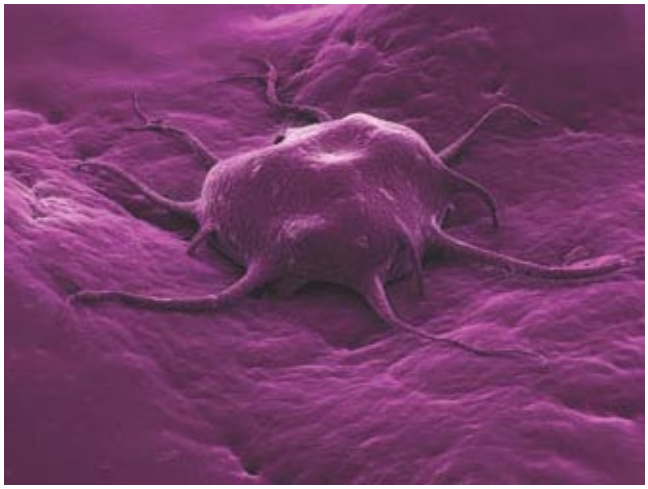


Visualization of full I2D human protein interaction database

Andrew Berchuck, M.D.
Duke University

Large-Scale Studies to Simultaneously Study Risk and Prevention

Dr. Andrew Berchuck and colleagues at Duke University initiated a large case-control study that considers genetic susceptibility, epidemiologic risk factors, and acquired genetic alterations to determine risk factors. The group is also approaching prevention through chemoprevention studies.



Dr. Berchuck and his team found that a specific polymorphism in the promoter of the progesterone receptor (the +331A allele) was associated with a strong decreased risk of endometrioid and clear cell ovarian cancers. There was also a slight association with decreased risk of the common ovarian serous tumors. These results suggest that progestins (synthetic progesterones) may be effective chemopreventive agents.

The researchers used chicken models to test candidate chemopreventive agents because chickens are the only animals that develop spontaneous ovarian cancer at a high rate. The research team performed an initial ovarian cancer chemoprevention trial in chickens and showed that levoneorestrel (a synthetic progesterone used as a contraceptive in humans) demonstrated a protective effect. The researchers also showed that the resulting progestin-mediated apoptosis in the ovarian epithelium was regulated by transforming growth factor-beta. Vitamin D enhanced these apoptotic effects in cell lines. The investigators are performing chemoprevention studies with vitamin D in chickens to determine if it will enhance the effects of levoneorestrel; specifically, progestins and vitamin D analogs are being tested.

David Gershenson, M.D.
M.D. Anderson Cancer Center

A Chemoprevention Approach That Combines Vitamins and Oral Contraceptives

Dr. David Gershenson of the M.D. Anderson Cancer Center is studying the chemopreventive effects of oral contraceptives and fentrinide (4-HPR), a synthetic vitamin A, in the rhesus macaque monkey model. The rhesus macaque could potentially be an excellent model for studying chemoprevention of ovarian cancer because these monkeys are close to humans in their cyclic menstrual pattern and ovarian function, structure, histochemistry, and response to hormones.

With funding from an **FY98 Program Project**, Dr. Gershenson and his research team found that this nonhuman primate model was an excellent model for ovarian cancer chemoprevention. Additionally, fluorescence spectroscopy appeared to be the best biomarker for following changes from chemopreventive agents optically. Furthermore, the investigators found that the combination of 4-HPR and oral contraceptives upregulated 4 out of 6 retinoid receptors, as well as ER expression, suggesting a potential mechanism for the chemopreventive effects of these treatments.

Thinking Differently about Ovarian Cancer—New Discoveries

Q. My wife was recently diagnosed with ovarian cancer. I know there is a lot of research going on, but what are some of the newest and most exciting discoveries? And how will they help patients?

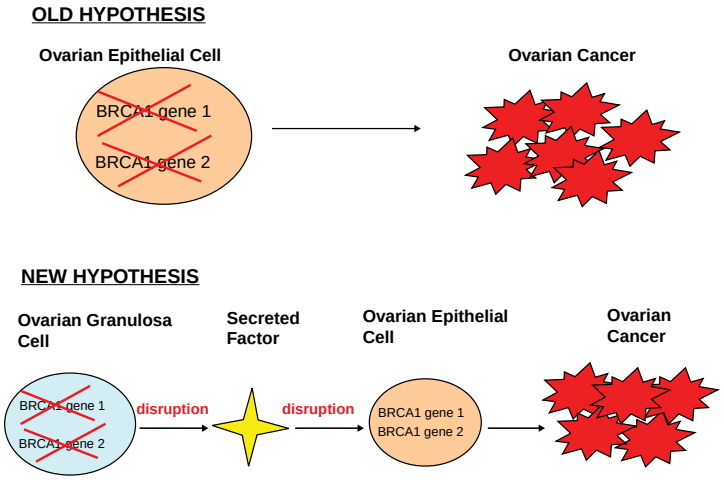
A. Discoveries in ovarian cancer are helping us to understand the mechanisms that underlie the development and progression of cancer.

OCRP researchers are thinking differently about target cells, animal models, and signaling pathways that are important for understanding ovarian cancer and ultimately helping patients. Their new ideas have led to unexpected and exciting findings.

Finding the Target Cells That Cause Ovarian Cancer

Dr. Louis Dubeau of the University of Southern California is searching for the specific cell type that causes ovarian cancer, particularly ovarian cancer involving mutant BRCA1 genes. Women with inherited mutations of BRCA1 have a 40 percent risk of developing ovarian cancer by age 70 and are also predisposed to breast and fallopian tube tumors. The conventional hypothesis is that BRCA1 is inactivated within the tumor cells themselves. However, Dr. Dubeau proposed a new theory that granulosa cells in the ovary are the critical cells affected by BRCA1 inactivation and that these cells then regulate the growth of the tumor cells. Granulosa cells normally produce sex hormones that regulate the ovulatory cycle, help oocyte (egg) cells develop, and influence cell growth.

With funding from an **FY03 Idea Development Award**, Dr. Dubeau and his colleagues inactivated the BRCA1 gene specifically in ovarian granulosa cells in a mouse model. Two-thirds of the animals developed serous adenomas in the ovaries and uterine horns. Serous tumors are commonly observed in women with BRCA1 mutations. The tumor cells looked like epithelial cells and had normal copies of the BRCA1 gene, suggesting that they were not derived from the granulosa cells. Instead, these findings suggest that tumor development occurred through a mechanism in which a factor was secreted by granulosa cells. Identifying this secreted factor could lead to new, more effective screening and prevention strategies based on blood-based detection of this substance. The factor may also provide a target for new therapies for treating ovarian cancer.

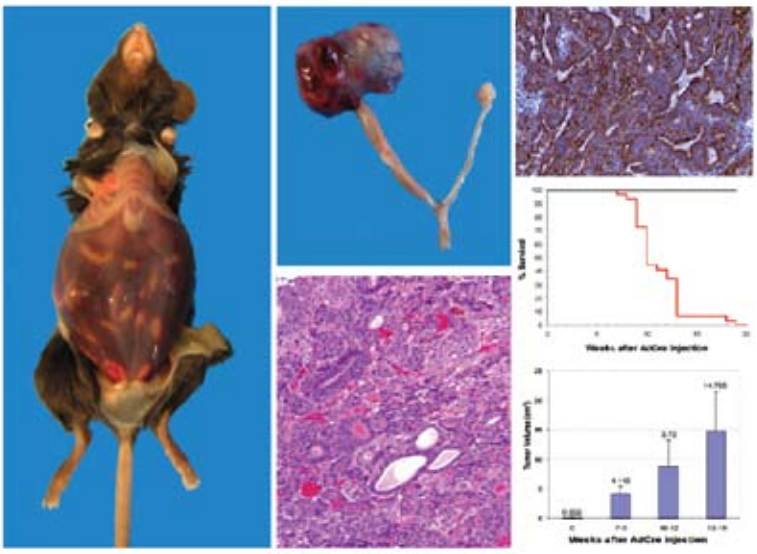


Rong Wu, M.D.
University of Michigan

New Animal Models to Study Ovarian Cancer

Drs. Rong Wu and Kathleen Cho of the University of Michigan are studying ovarian endometrioid adenocarcinoma (OEA), which is the second most common of four major types of epithelial ovarian cancer (the others are serous, clear cell, and mucinous). With funding from an **FY03 New Investigator Award**, Dr. Wu and her colleagues showed that mutations predicted to deregulate the canonical Wnt signaling pathway (via mutant CTNNB1/β-catenin) and the PI3K/Pten/Akt signaling pathway (via mutant PIK3CA and/or PTEN) often occurred together in OEAs. The subsets of OEAs with these gene mutations were usually low-grade, low-stage tumors. In contrast, mutations in the TP53 tumor suppressor gene were common in high-grade OEAs but infrequent in the low-grade tumors. Mutations of K-RAS were relatively uncommon in OEAs and never observed together with PTEN mutations.

The researchers generated a unique mouse model of OEA based on deregulation of Wnt and PI3K/Pten/Akt signaling specifically in the murine ovarian surface epithelium. The mice developed tumors with similar morphology, biological behavior, and gene expression patterns to human OEAs. This model system could be highly useful for preclinical testing of new therapies that target these signaling pathways in ovarian cancer cells. Such therapies may be particularly beneficial for women with recurrent disease.

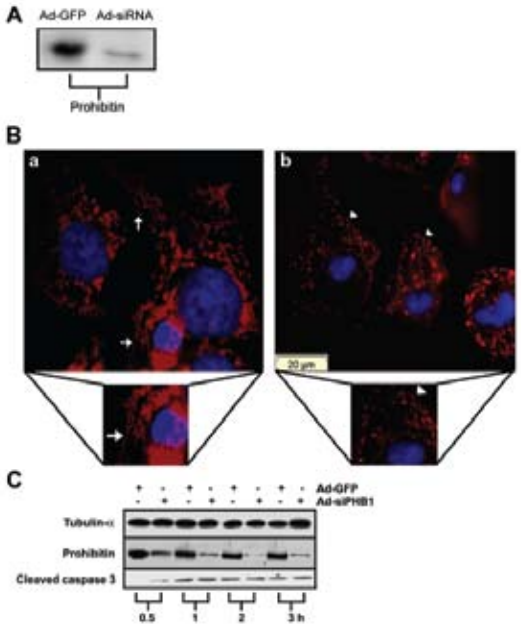


The left panel: The Apc loxP/LoxP; Pten loxP/LoxP mouse developed ovarian carcinoma after APC and PTEN inactivation with massive abdominal distension by hemorrhagic ascites, which was similar to women with OEAs. Top-middle: On the right is mouse ovarian carcinoma and on the left is normal ovary. Bottom-middle: Mouse tumor is similar to human OEAs morphologically, which showed distinct gland formation. Top-right: Mouse OEA-like tumor showed strong cytokeratin-8 immunostaining confirming the epithelial differentiation. Middle-right: Mouse OEA-like tumors showed volume increase once established, doubled roughly every 3 weeks. Bottom-right: Mouse OEA-like tumors were grossly apparent within 6 weeks after APC and PTEN inactivation and all animals died of tumor burden within 19 weeks.

Winston Thompson, Ph.D.
Morehouse School of Medicine

New Signaling Pathways Prohibitin and Estrogen-Mediated Signaling

Dr. Winston Thompson of the Morehouse School of Medicine is studying and characterizing the antiproliferative and tumor-suppressive properties of prohibitin. Prohibitin is a candidate therapeutic target for several disease states, including inflammation, obesity, and cancer. Prohibitin is believed to be a tumor suppressor gene and has been associated with G1/S cell cycle arrest; however, little is known about the function of prohibitin during growth and differentiation of the ovarian epithelium. With funding from an **FY02 Idea Development Award**, Dr. Thompson discovered the mechanisms by which prohibitin encourages growth arrest in ovarian cancer cells. Based on recent findings indicating that the protein repressor of estrogen receptor activity (REA) is a prohibitin splice variant, Dr. Thompson constructed experiments to determine the role of prohibitin as well as REA in growth suppression by estrogen antagonists. Dr. Thompson's studies showed that prohibitin and REA are expressed in ovarian cancer cells and physically interact with each other in both the mitochondria and nucleus. These findings are significant for the future development of the next generation of improved drug therapy for ovarian cancer.



Adenovirus-Directed Knock-Down of Prohibitin Is Associated with Destabilization of Mitochondrial Integrity and Chemosensitivity in Ovarian Cancer Cells. A, OVCAR8 cells were infected with Ad-siRNA prohibitin (MOI = 80) or Ad-eGFP (MOI = 80) for 2 h and maintained in culture for 48 h. Expression of prohibitin protein level was assayed using Western blotting techniques. B, Effect of Ad-siRNA-PHB1 on the morphology of the mitochondria. Two days after infection with vector only (a) or PHB1 siRNA (b), OVCAR8 cells were fixed and immunostained with prohibitin antibody. Note arrow depicting long tubular mitochondrial network (a) and arrowhead showing punctiform mitochondria (b). C, Western blot analysis was conducted to detect levels of prohibitin and cleaved caspase-3, 0.5, 1, 2, and 3 h post-treatment with 1uM STS. Tubulin was used as an internal control. Prohibitin knockdown enhances apoptosis in OVCAR8 cells. Data are representative of three individual experiments. Bar = 20 mm

Telomerase and Apoptosis

Dr. Patricia Kruk of the University of South Florida is studying the mechanisms of telomerase and apoptosis. Dr. Kruk hypothesized that telomerase re-activation may confer resistance to apoptosis resulting in increased cancer cell survival and decreased cellular sensitivity to chemotherapeutic treatment.

With funding from an **FY01 Program Project**, Dr. Kruk's team showed that telomerase enhanced ovarian cell survival and reduced caspase 3-mediated apoptosis. Furthermore, telomerase-mediated anti-apoptosis was JNK-dependent. Finally, Dr. Kruk's team showed that increased telomerase, specifically the hTERT catalytic component, caused increased expression of the anti-apoptotic mitochondrial protein, Bcl-2.

Dr. Kruk's group is pursuing studies to develop a diagnostic test to detect ovarian cancer based on elevated urinary levels of Bcl-2. The researchers have filed a patent on this invention and received an **FY06 Idea Development Award** to continue developing this test.

Aurora Proteins

Dr. Jin Cheng of the University of South Florida is discovering the role of the Aurora-A oncogene in ovarian cancer signal transduction and chemoresistance. Aurora-A regulates centrosomes and mitosis. Disruptions in Aurora-A are believed to cause genomic instability in tumor cells.

With funding from an **FY04 Idea Development** Award, Dr. Cheng's team showed that Aurora-A protected ovarian cancer cells from apoptosis induced by chemotherapeutic agents and activated the Akt pathway in a p53-dependent manner. Overexpression of Aurora-A caused cells to become resistant to cisplatin (CDDP), etoposide, and paclitaxel-induced apoptosis. It also stimulated Akt1 and Akt2 activity in wild-type p53 but not p53-null ovarian cancer cells. In contrast, knockdown of Aurora-A by RNAi sensitized cells to CDDP-induced apoptosis and decreased phospho-Akt levels in wild-type p53 cells.

These results suggest that because Aurora-A activates Akt and because Aurora-A-induced chemoresistance is p53 dependent, Akt inhibitors or Aurora-A inhibitors could be an effective strategy for overcoming Aurora-A-induced chemoresistance in ovarian cancer cells expressing wild-type p53.

Thinking Differently—Innovative Technologies

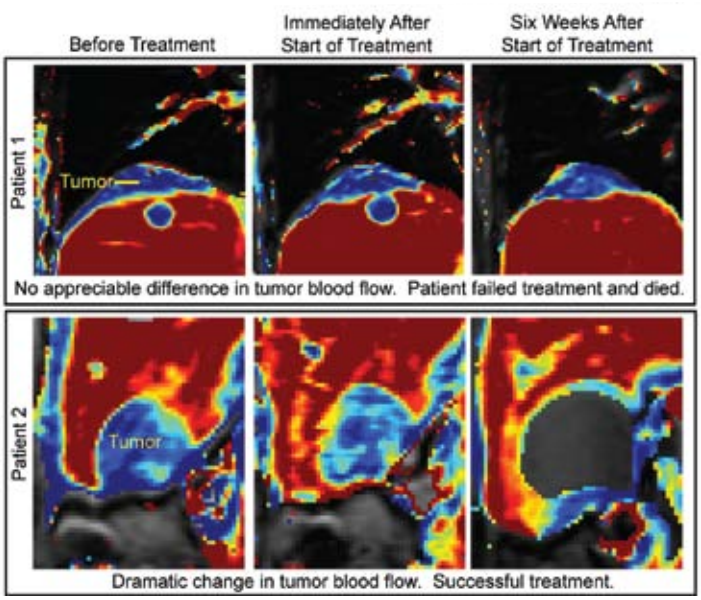
Q. I am an ovarian cancer patient. What are some of the most exciting new technologies being developed by industry? And how can they be applied to help patients?

A. The Congressionally Directed Medical Research Programs (CDMRP) participates in the Army Small Business Innovation Research/Small Business Technology Transfer programs to leverage research and product development not supported elsewhere by the CDMRP. Three success stories are highlighted on the following pages.

The OCRP is thinking differently about technologies and partnerships with small businesses.

New Imaging Technologies

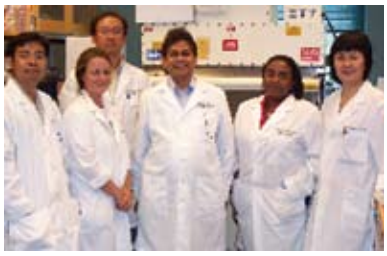
Dr. David Kynor and his colleagues at Creare are developing enhanced imaging methods based on dynamic contrast enhancing-magnetic resonance imaging for imaging of vascular function and angiogenesis associated with cancer and wound healing. The overall goal is to use this technology for screening and detection of early-stage ovarian cancer. Dr. Kynor plans to first test and optimize this technology in an animal model and then move to human testing.



Contrast-Enhanced MRI for Evaluation of Ovarian Cancer Treatment

New Nanoparticle-Based Self-Lighting Photodynamic Therapy

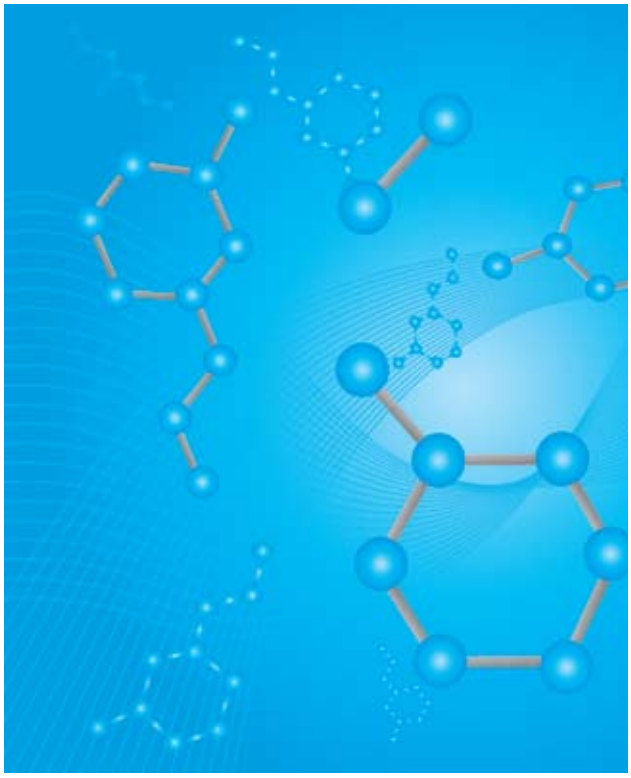
Dr. Shaopeng Wang of ICx Nomadics Inc. is developing a nanoparticle self-lighting photodynamic therapy (PDT) for ovarian cancer treatment. The overall goal of the project is to improve the efficiency of nanoparticle self-lighting PDT and to reduce the risks to cancer patients. The team successfully synthesized nanoparticles and conjugated them to photosensitizers. The team found which specific conjugated nanoparticles showed the least toxicity and is testing these compounds in mouse models of ovarian cancer.



Members of Weidong Xu, M.D., (left) and Shyam Mohapatra, Ph.D., (center) research group

New Nanotechnology-Based Gene Therapy System

Dr. Weidong Xu of Transgenex Nanobiotech, Inc. and Dr. Shyam Mohapatra of the University of South Florida are developing a novel gene therapy strategy combining nanotechnology and the Sleeping Beauty (SB) transposon-based nonviral gene transfer system to achieve targeted delivery of DNA-based drugs to cancer cells for treatment of ovarian cancer. The nanoparticles are composed of chitosan, a natural biocompatible polysaccharide extracted from crustacean shells. The team discovered that the atrial natriurectic peptide signaling pathway is involved in tumorigenesis of several types of cancers including ovarian cancer. They identified two natriuretic peptides (regulators of sodium and water balance), NP73-102 and vessel dilator (VD), as candidate cancer drugs. Both NP73-102 and VD downregulate NFκB and ERK-1/2 activities. The researchers found that stable expression of NP73-102 or VD from chitosan-SB nanocomplexes has the potential to provide protection against ovarian cancer in a mouse model.



Thinking Differently about Research Resources

Q. I am an ovarian cancer patient. My doctor talked with me about providing some blood samples to be used in research. What will happen to my samples? And what will they be used for?

A. An important goal of the OCRP is to establish sustained shared resources for studying ovarian cancer. The OCRP funded Program Projects that met the goal of developing critical resources, including tissue repositories with clinical data, databases, biomarkers, cell lines, and animal models. However, other OCRP award mechanisms, such as the Idea Development and New Investigator Awards have also generated new research resources. Table V-1 highlights some of the OCRP-supported investigators that have developed critical research resources for the ovarian cancer research community.

Table V-1. OCRP-Supported Research Resources

Principal Investigator	Research Resource
Dr. Nicole Urban	Repository with over 6,000 individually identified ovarian tissue specimens
Dr. David Bowtell	Multicenter population-based resource involving collection of linked epidemiologic and clinical data and biospecimens from 1,000 cases and 1,200 matched controls (1,719 questionnaires, 1,694 blood samples, and 1,061 frozen tissue samples)
Dr. Beth Karlan	Human ovarian tissue and clinical database containing ovarian carcinomas (152) and benign ovaries (110)
Dr. Samuel Mok	New biomarkers for early-stage ovarian cancer
Dr. Igor Jurisica	Computational tools and methods for analysis of complex biochemical, biological, and clinical data on epithelial ovarian cancer at no cost to the public
Drs. Gus Rodriguez and Patricia Johnson	Chicken models of ovarian cancer
Dr. Tyler Jacks	Mouse model of ovarian cancer associated with endometriosis
Dr. Louis Dubeau	Mouse model with homozygous BRCA1 knockout restricted to ovarian granulosa cells
Dr. Mary Daly	Book, "Ovarian Cancer Risk-Reducing Surgery: A Decision-Making Resource" (available to the public at no cost)
Dr. Santo Nicosia	Ovarian cancer tissue repository with more than 600 samples
Dr. Kathleen Cho and Dr. Rong Wu	Mouse model of OEA

The OCRP is thinking differently about developing research resources for the community.

Nicole Urban, Sc.D.
Fred Hutchinson Cancer Research Center
FY05–07 Integration Panel Member

"The OCRP is perhaps the most important program nationally in ovarian cancer research. In a field with very limited funding, the OCRP has been able to have a very significant scientific impact. A number of leaders in translational ovarian cancer research in the ovarian SPORE program at NCI were first funded by the OCRP; many of these investigators now serve on the OCRP Integration Panel. It is a pleasure and an honor to serve with these distinguished scientists who are committed to reducing the morbidity and mortality associated with this disease, and who ensure that the OCRP dollars support cutting-edge work with the potential for clinical impact."

The Program Today

Fiscal Year 2006 Summary

Congress appropriated $10M to continue the OCRP in FY06. The program offered three award mechanisms (Concept, HBCU/MI Collaborative Research, and Idea Development Awards) to make an impact on critical needs within the ovarian cancer community, understanding tumor biology/etiology, preclinical development of targeted therapeutics, and improved early detection/diagnosis of ovarian cancer. A total of 443 proposals was received across the three award mechanisms, as illustrated in Table V-2, and 22 awards were made. These 22 awards encompass basic, clinical, and research resources as shown in Figure V-2.

Table V-2. Funding Summary for the FY06 OCRP

Categories and Award Mechanisms	Proposals Received	Awards	Investment
Innovative Research			
Concept	328	11	$1.39M
Idea Development	110	10	$6.65M
Research Resources			
HBCU/MI Collaborative Research	5	1	$0.84M
TOTAL	443	22	$8.88M

Fiscal Year 2006

443 Proposals Received

$10M in Appropriations

22 Awards

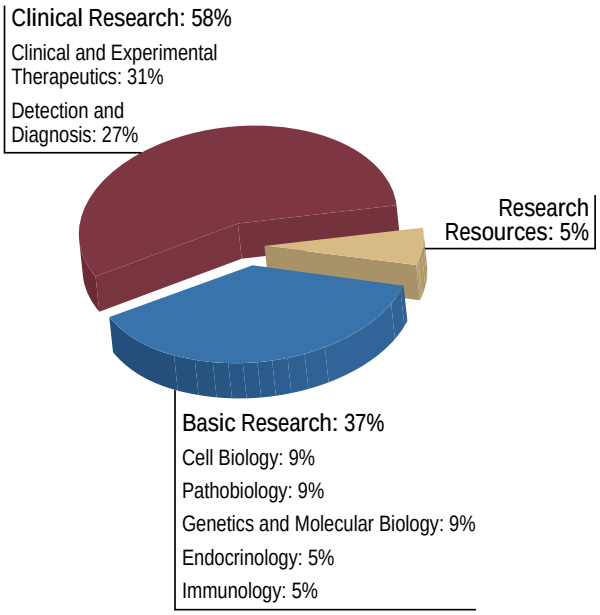


Figure V-2. FY06 OCRP Portfolio by Research Area

The Vision for Fiscal Year 2007

Congress again appropriated $10M to the OCRP in FY07. The program continued its history of thinking differently and defined a unique niche within the research community by offering two original award mechanisms, the HBCU/MI Fellowship Award and the Translational Partnership Award.

- The HBCU/MI Fellowship Award is intended to support a mentored training and research experience for HBCU/MI doctoral-level faculty members who aim to develop productive careers in ovarian cancer research.
- The Translational Research Partnership Award targets research collaborations between laboratory scientists and clinicians to address a central problem or question in ovarian cancer in a manner that would be less readily achievable through approaches based in a single laboratory.
- The intent of the Concept Award is to support new ideas and the exploration of innovative concepts or theories in ovarian cancer.

The program continued to support innovative and unconventional research ideas pertaining to ovarian cancer through Concept Awards. A total of 331 proposals was received across the three award mechanisms, and approximately 40 awards are expected. Appendix B, Table B-4, summarizes congressional appropriations and the investment strategy executed by the OCRP for FY06 through FY07.

The OCRP - Thinking Differently

Since its inception, the OCRP has been filling unique niches by encouraging research in areas that are being unmet within the ovarian cancer research community. Below is a depiction of new mechanims introduced by the OCRP since its inception.