

CONGRESSIONALLY DIRECTED
MEDICAL RESEARCH PROGRAMS:
PARTNERING FOR A CURE

V. Ovarian Cancer Research Program





Vision

To eliminate ovarian cancer.

Mission

To support innovative, integrated, multidisciplinary research efforts that will lead to better understanding, detection, diagnosis, prevention, and control of 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 2006, approximately **20,180** women will be diagnosed with ovarian cancer in the United States. 🌸 An estimated **15,310** women will die from ovarian cancer this year. 🌸 The 5-year survival rate for all stages of ovarian cancer is approximately **45%**. However, local ovarian cancer has a **94%** 5-year relative survival rate, thus emphasizing the need for early diagnosis.¹



¹ American Cancer Society - *Cancer Facts and Figures*, 2006.



Signs and Symptoms

Ovarian cancer often is not associated with any obvious signs or symptoms until late in its development. However, some indicators of ovarian cancer may include the following:

- ❖ Enlargement of the abdomen
- ❖ General abdominal discomfort and/or pain (gas, pressure, indigestion, distention)
- ❖ Abnormal bleeding from the vagina (although rare)
- ❖ Urinary symptoms

While these nonspecific symptoms are not always related to a serious condition, many women with advanced ovarian cancer recall experiencing these symptoms.²



² American Cancer Society - *Cancer Facts and Figures*, 2006.

Program Background

The Department of Defense (DOD) Ovarian Cancer Research Program (OCRP) was established in fiscal year 1997 (FY97) by Appropriations Conference Committee Report No. 104-863, which provided \$7.5 million (M) for research in ovarian cancer. During the 1990s, ovarian cancer advocates launched a grassroots campaign to increase funding for ovarian cancer research. In response to these efforts and heightened public awareness for increased research, Congress appropriated \$101.7M to the OCRP from FY97 to FY06. Since its inception, the OCRP has been impacting 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 108 awards have been made through FY05 across the categories of research, training/recruitment, and research resources (see Figure V-1, OCRP History).

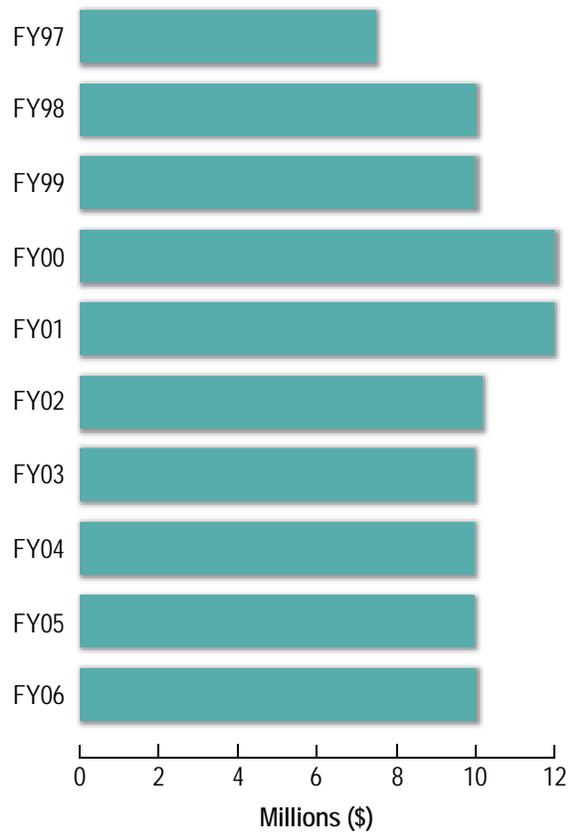


Figure V-1. OCRP History



The Program Today

Fiscal Year 2005 Summary

Congress appropriated \$10M to continue the OCRP in FY05. The program retained the Idea Development Award and also introduced two new award mechanisms, the Historically Black Colleges and Universities/Minority Institutions (HBCU/MI) Collaborative Research Award and Pilot Award. All three award mechanisms placed emphasis on tumor biology/etiology, preclinical development of targeted therapeutics (excluding clinical trials), and early detection/diagnosis of ovarian cancer. The HBCU/MI Collaborative Research Award was designed to foster collaborations at an investigator level between an HBCU/MI and another institution. The Pilot Award was intended to support highly innovative, high-risk/high-reward ovarian cancer research from established investigators with less than 3 years of experience in the field of ovarian cancer or from junior faculty within 5 years of their last training experience. A total of 225 proposals were received across the three award mechanisms, as illustrated in Table V-1, and 16 awards were made. As illustrated in Figure V-2, the FY05 OCRP has developed a research portfolio that encompasses basic, clinical, and population-based research.

Fiscal Year

2005 225 Proposals Received
 2005 \$10M in Appropriations
 2016 Awards

Table V-1. Funding Summary for the FY05 OCRP

Categories and Award Mechanisms	Proposals Received	Awards	Investment
Innovative Research			
Idea Development	135	8	\$6,139,655
Pilot	84	7	\$2,208,343
Research Resources			
HBCU/MI Collaborative Research	6	1	\$630,000
TOTAL	225	16	\$8,977,998

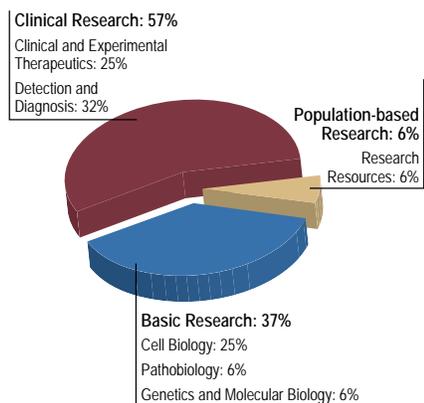


Figure V-2. FY05 OCRP Portfolio by Research Area

Fiscal Year 2006 Summary

Congress appropriated \$10M to continue the OCRP in FY06. The program retained the Idea Development Awards and the HBCU/MI Collaborative Research Awards that were offered in the previous fiscal year and also introduced Concept Awards. The intent of both the Idea Development and Concept Awards focuses on the innovation of the research ideas and their impact on the field of ovarian cancer. All three award mechanisms placed emphasis on tumor biology/etiology, preclinical development of targeted therapeutics (excluding clinical trials), and early detection/diagnosis of ovarian cancer. A total of 443 proposals were received across the three award mechanisms, as illustrated in Figure V-3, and approximately 20 awards are expected. Appendix B,

Table B-4, summarizes congressional appropriations and the investment strategy executed by the OCRP for FY05 through FY06.

Fiscal Year **2006**
443 Proposals Received
\$10M in Appropriations
~20 Awards

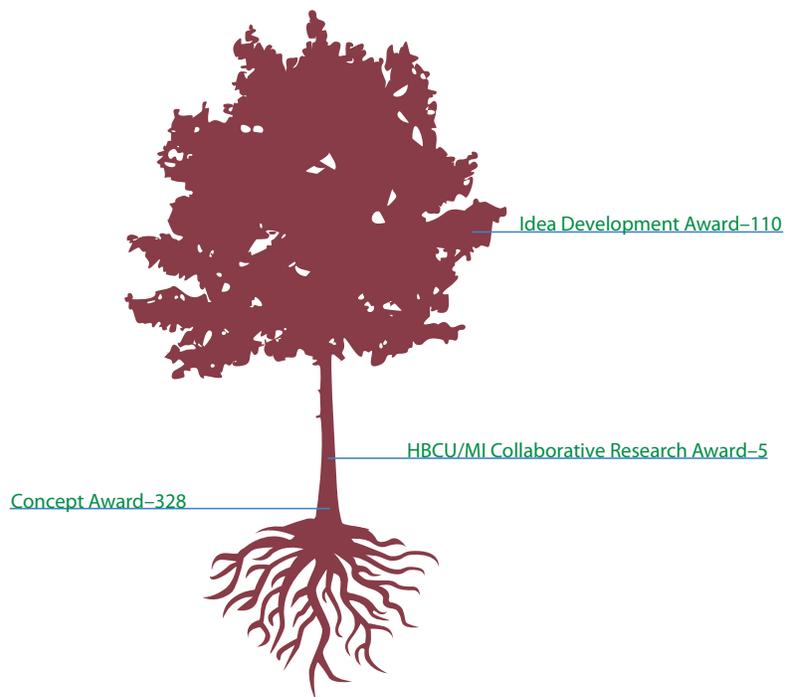


Figure V-3. Award Mechanisms Offered and Proposals Received for the FY06 OCRP



Making an Impact: The Best People

Outstanding people—from scientists and research managers to consumer advocates—have impacted the field of ovarian cancer research. The OCRP recognizes the contributions from numerous people that have made this program a success.

MS. MARY SCROGGINS, FY06 CONSUMER IP MEMBER

"Having participated in the OCRP since its beginning, I continue to be impressed with and encouraged by the quality of proposals received and the excellence and dedication of reviewers—advocates and researchers—who so generously give of their time and share their expertise to ensure that the best, most promising proposals are funded. Program-by-program, OCRP is making a difference in the lives of women and families fighting ovarian cancer and preemptively—through prevention projects—in the lives of women to-date unaffected."



Mrs. Cindy Melancon, former OCRP Integration Panel (IP) member (deceased) and Ms. Patricia Goldman, current OCRP IP member, address the first meeting of the Ovarian Cancer National Alliance in 1998

Consumer Advocate Participation

Taking their cue from the successful lobbying efforts of breast cancer advocates, ovarian cancer advocates pressed Congress for appropriations for ovarian cancer research in the 1990s. In response, Congress appropriated \$7.5M for an ovarian cancer research program in FY97. The DOD convened a stakeholders meeting in April 1997 to plan the new program. In addition to scientists and clinicians, ovarian cancer advocates from around the United States were invited to the meeting. Some of these advocates had begun to communicate with each other by telephone and mail, but few had met. The OCRP stakeholders meeting offered an important opportunity for these women to share ideas and network. Future meetings of the OCRP brought and continue to bring together consumer advocates in the ovarian cancer community.



Ovarian cancer activists form a sea of teal at the 1998 March on Washington as part of "Coming together to Conquer Cancer"



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 decisions. More than 75 consumer advocates have served on peer and programmatic review panels for the OCRP 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 back to their 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 Chapter I.

MS. AMY MURRAH

FY06 OCRP CONSUMER PEER REVIEWER

"Being a part of this amazing program has given me the opportunity to share my opinions on research proposals that could potentially make a difference in the lives of women battling ovarian cancer or those who've not been diagnosed. I would go the distance anytime I can to make sure no other young women suffer like I did."



Consumer reviewers Ms. Amy Murrah and Ms. Annie Shuma at the FY06 OCRP Peer Review meeting

MS. MARIA CIESLA, FY06 OCRP CONSUMER PEER REVIEWER

"Those living with ovarian cancer wonder how much progress is truly being made in the research of early detection and gentler therapeutic approaches. Having had the privilege of serving as a consumer reviewer on two OCRP panels, I am more hopeful than ever for the coming breakthroughs in both areas of research. Hundreds of investigators through so many novel disciplines have and continue to explore ways to bring their theories to the clinical setting. Then the OCRP panels of the CDMRP bring together the most distinguished and respected scientists and physicians along with excited and passionate consumer reviewers—as peers—to review and thoughtfully discuss the many submitted proposals, scoring the best for further funding considerations. An important and validating aspect of this excellent process is that the scientific reviewers and the consumer reviewers learn from each other. If only all living with this insidious disease could partake in this process, there would be renewed hope in their hearts and in our 'community!'"



Consumer reviewers Ms. Maria Ciesla, Ms. Renae Plummer, and Ms. Marianne Mills share a laugh at the FY06 OCRP Peer Review Meeting

MS. MARIANNE MILLS, FY06 OCRP CONSUMER PEER REVIEWER

"'We are not mice!' This comment was interjected into a debate between two scientific reviewers about the severe toxicity of a proposed treatment to laboratory mice. After several minutes of discussion, I felt compelled to remind the panel that it is women who are facing or will face ovarian cancer, not mice, who will ultimately be affected by the outcomes of the peer review. After the session, several scientists thanked me. As a consumer reviewer, my opinions were valued, and my participation kept the panel focused on the needs of the ovarian cancer constituency. It was an exhilarating experience and an opportunity to make a difference."



Integration Panel Members

The OCRP IP, composed of visionary and innovative scientists, clinicians, and consumer advocates, sets the annual program vision and develops investment strategies that meet the needs of the research and consumer communities. The OCRP IP also reviews proposals and recommends the most meritorious and programmatically relevant proposals for funding (for more information about the functions of the IP see Chapter I).

Fiscal Year 2006 IP Members

*JEFFREY BOYD, PH.D. (CHAIR), ANDERSON CANCER INSTITUTE OF THE
MEMORIAL HEALTH UNIVERSITY MEDICAL CENTER*

STEPHEN RUBIN, M.D. (CHAIR EMERITUS), THE UNIVERSITY OF PENNSYLVANIA MEDICAL CENTER

MARY SCROGGINS, M.A. (EXECUTIVE COMMITTEE MEMBER-AT-LARGE), IN MY SISTER'S CARE

JAMES P. BASILION, PH.D., CASE WESTERN RESERVE UNIVERSITY

KATHLEEN R. CHO, M.D., UNIVERSITY OF MICHIGAN MEDICAL SCHOOL

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

NITA J. MAIHLE, PH.D., YALE UNIVERSITY SCHOOL OF MEDICINE

NYRVAH RICHARD, IN MY SISTER'S CARE

GUSTAVO RODRIGUEZ, M.D., NORTHWESTERN UNIVERSITY FEINBERG SCHOOL OF MEDICINE

MICHAEL SEIDEN, M.D., PH.D., MASSACHUSETTS GENERAL HOSPITAL

NICOLE URBAN, SC.D., FRED HUTCHINSON CANCER RESEARCH CENTER

S. DIANE YAMADA, M.D., UNIVERSITY OF CHICAGO HOSPITALS

Scientific Community

The OCRP funds exceptional scientists and clinicians that are committed to impacting the field of ovarian cancer. To date, more than 120 researchers have dedicated their efforts as advisors, reviewers, and scientists to fulfilling the program's mission and vision. The remainder of this chapter is a cross-section of OCRP-supported research progress that is making a difference in the fight against ovarian cancer.



JEFFREY BOYD, PH.D., FY06 OCRP IP CHAIR

“Because of its unique mandate and resources, the OCRP has had a profound impact in the field of ovarian cancer research. Unlike other major funding agencies, by soliciting grant applications focused specifically on the ovarian cancer problem, we have encouraged some of the best and brightest in the field to develop novel hypotheses and models that will translate into decreased morbidity and mortality from this disease. We are especially proud of the funding initiatives on Program Projects and New Investigators Awards that have sown the seeds of future ovarian cancer research programs and individual investigators that would not otherwise have existed without support from the CDMRP/OCRIP. I am honored to have had the opportunity to be associated with this outstanding organization and the fight against ovarian cancer.”



LINDA MALKAS, PH.D., FY06 OCRP PEER REVIEW PANEL CHAIR

"It is an honor for me to be a part of this program. The advocates, consumer and scientific study section participants, and other program team members are an inspiration to me. I marveled at how the scientific and consumer reviewers put their minds and hearts to work for days with only one mission, that is to find the research that is going to strike at this disease. When we finished with our reviews of all of the submitted applications this year, we all felt that we had found several real diamonds in the research. Speaking for the study section, we believe that something wonderful is going to come from this program."

RICHARD BRITTEN, PH.D., FY06 OCRP PEER REVIEW PANEL CO-CHAIR

"The inspiration for most cancer researchers is the hope that we will discover something that will help the cancer patients we see every day at work. Unfortunately, when we go to family gatherings and get asked "Have you cured cancer yet?" we always have to reply with the very apologetic and uninspiring "Not yet, but we are working on it!" However, now that I have been part of the review process for the CDMRP ovarian cancer initiative, I can tell my relatives "I haven't, BUT one of my colleagues is working on this really clever idea that probably will!" It's a real privilege to read the excellent proposals we receive and to get critical input from real cancer survivors on proposals that impact them...collectively we can make a huge impact on the lives of women with ovarian cancer."



Making an Impact: Research Resources

From the outset, one of the main goals of the OCRP was to establish sustained shared resources that could be used to study ovarian cancer. This goal was addressed by funding a total of 16 Program Projects in FY97, FY98, FY00, and FY01. These projects have developed biological and informational resources critical for moving ovarian cancer research forward.





OVARIAN TISSUE AND CLINICAL DATABASE TO STUDY OVARIAN CANCER ETIOLOGY

An FY98 Program Project Award to Beth Karlan of the University of California, Los Angeles supported the establishment of a human ovarian tissue and clinical database. During the 4 years of this award, the facility banked 152 ovarian carcinomas and 110 benign ovaries, of which one-third are from women with either a family history of ovarian cancer or a known BRCA mutation. In addition, the tissue resources of the facility were linked to clinical, demographic, and epidemiological data to enable clinical correlation with laboratory results.

MULTICENTER POPULATION-BASED RESOURCE TO EXAMINE THE MOLECULAR EPIDEMIOLOGY OF OVARIAN CANCER

David Bowtell of the Peter MacCallum Cancer Centre in Melbourne, Australia, was awarded a Program Project in FY00 to establish a multicenter population-based resource to collect biospecimens with linked epidemiological and clinical data from cases and matched controls. More than 1,800 cases and 1,000 controls have been recruited, and more than 1,000 fresh-frozen tumor samples have been collected. Expression analysis of such a large set of matched specimens makes it possible to study associations among epidemiologic risk factors, low-risk genes, and histologic and novel molecular subtypes of ovarian cancer. Since Australia uses socialized, registered medical care, all of these individuals will be followed for their lifetimes. Resources such as these support better understanding of the etiology of ovarian cancer, which can lead to the discovery of diagnostic and prognostic indicators of the disease.



Three recipients of Program Projects—M.D. Anderson Cancer Center, Fred Hutchinson Cancer Research Center, and Fox Chase Cancer Research Center—subsequently were awarded National Cancer Institute Specialized Program of Research Excellence (SPORE) grants to further support translational research approaches to this disease. In addition, Massachusetts General Hospital was awarded a SPORE award based on the results it achieved through its Program Project and its OCRP Institutional Training Grant. The Institutional Training Grant awarded in FY02 trained six postdoctoral researchers, including four physician–scientists. Training Program Director Dr. Michael Seiden leveraged the success of this OCRP funding to compete successfully for a 5-year T32 grant from the National Cancer Institute to provide continuing support.





Making an Impact: Animal Models of Disease

Animal models of ovarian cancer provide powerful resources for investigators to study disease mechanisms and test new therapeutics before human clinical trials. The OCRP has funded the development of several animal models that have enabled investigators to conduct important studies that were not possible previously. Two animal models of ovarian cancer are summarized on the following page.



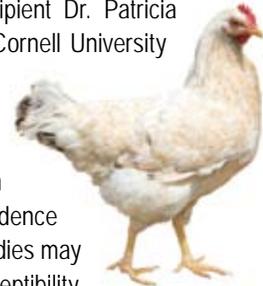
CHEMOPREVENTION OF OVARIAN CANCER



Experimental studies have shown that the vitamin A analog fenretinide may reduce the risk of ovarian cancer. FY98 Program Project Award recipient Dr. David Gershenson of M.D. Anderson Cancer Center is employing a comprehensive strategy to study the chemopreventive effects of fenretinide in cell lines, tissues, monkeys, and women. The rhesus monkey is genetically similar to humans and is the only mammal that has a menstrual cycle similar to that of women. Dr. Gershenson and his team have developed this animal model to further understand how fenretinide can prevent ovarian cancer. The group has demonstrated synergistic effects of fenretinide in combination with oral contraceptives in rhesus monkeys and identified potential intermediate biomarkers for ovarian cancer chemoprevention trials using these drugs. Their results suggest that the combination of fenretinide and oral contraceptives upregulated four out of six retinoid receptors as well as estrogen receptor beta expression. As part of this Program Project, a clinical trial of fenretinide was performed in women at high risk for developing ovarian cancer. Participants were monitored for expression of biomarkers for cell proliferation and apoptosis in response to fenretinide treatment. Findings from this clinical trial in humans plus the results of the animal studies can be used to design larger randomized prospective trials to determine the true preventive activity of fenretinide, oral contraceptives, and other agents.

CHARACTERIZATION OF THE CHICKEN OVARIAN CANCER MODEL

Chickens are the only animals that have developed spontaneous ovarian cancer at a high rate. FY99 Idea Award recipient Dr. Gus Rodriguez of the Evanston Northwestern Healthcare Research Institute is evaluating the chicken ovarian cancer animal model and determining its relevance to human ovarian cancer. Dr. Rodriguez and his team have accumulated 1,400 chicken reproductive tracts including 140 with adenocarcinomas and gathered valuable data regarding the natural history of these tumors. A histologic classification for chicken ovarian cancers is under way, which is critically important to the widespread use of this animal model for ovarian cancer research. FY99 New Investigator Award recipient Dr. Patricia Johnson and colleagues at Cornell University also are studying ovarian cancer in chickens through the use of two related genetic chicken strains, which differ in the spontaneous incidence of ovarian cancer. These studies may uncover the differential susceptibility to ovarian cancer.





Making an Impact: Etiology and Tumor Biology

Before the rational design of therapeutics and treatments can progress, a thorough understanding of the way in which ovarian cancer develops and progresses is needed. Once defined, the unique features and requirements of ovarian cancer serve as targets of opportunity to attack the cancer, as well as important diagnostic tools for detection and prognosis. Four noteworthy OCRP Idea Development Awards funded between FY02 and FY04 have contributed to the understanding of ovarian cancer etiology and biology.

TIPPING THE BALANCE: KLF6 ISOFORMS AND OVARIAN CANCER

FY02 Idea Development Award recipient Dr. John Martignetti of the Mount Sinai School of Medicine examined the tumor suppressor KLF6, which is functionally inactivated in approximately half of all epithelial ovarian cancers. Dr. Martignetti found that the KLF6 gene still is present in these cancers but that the protein product is altered due to an alternative splicing event. The splice variant KLF6-SV1 does not retain its normal function, causing increased proliferation of cells. These findings increase our understanding of ovarian cancer progression and metastasis and suggest that targeting KLF6-SV1 to tip the balance in favor of KLF6 could be a successful therapy for ovarian cancer.

NOVEL CELL DEATH REGULATORY PROTEIN

The Mayo Clinic's Dr. Viji Shridhar focused on the loss of expression of a novel protein in ovarian cancer, transcription elongation factor A (SII)-like 7 (TCEAL 7). With support from an FY03 Idea Development Award, Dr. Shridhar showed that the TCEAL 7 gene is silenced by hypermethylation in ovarian cancer. Inducing expression of TCEAL 7 in ovarian cancer cells induces apoptosis of those cells and reduces colony formation. Dr. Shridhar's results suggest that TCEAL 7 is a cell death regulatory protein that frequently is inactivated in ovarian cancers and may function as a tumor suppressor.

THE ROLE OF EPHA2 IN OVARIAN CANCER

The transmembrane receptor tyrosine kinase EphA2 is located on chromosome 1p36.1, which is a hotspot for rearrangements in many human cancers including ovarian cancer. With funding from an FY03 Idea Development Award, Dr. Anil Sood of the M.D. Anderson Cancer Center has demonstrated that EphA2 is overexpressed in most ovarian cancers and that the expression level of EphA2 correlates with tumor grade and may serve as a predictive indicator of aggressive ovarian cancer behavior. Dr. Sood has shown that silencing the expression of EphA2 in orthotopic tumors in mice dramatically reduces their growth, and he is developing EphA2 silencing for human clinical trials.

AURORA-A ONCOGENE: A TARGET FOR OVARIAN CANCER INTERVENTION

FY04 Idea Development Award recipient Dr. Jin Cheng of the University of South Florida studied the frequent activation and overexpression of the Aurora-A oncogene in human primary ovarian tumors. He showed that Aurora-A activates Akt and that ectopic expression of Aurora-A makes ovarian cancer cells resistant to cisplatin, etoposide, and paclitaxel-induced apoptosis. Both Aurora-A capabilities are dependent on p53. His results suggest that inhibition of Akt may be an effective means of overcoming Aurora-A-associated chemoresistance in ovarian cancer cells expressing wild-type p53.

Members of Dr. Anil Sood's Research Group





Making an Impact: Detection and Diagnosis

Women developing ovarian cancer do not have any obvious early symptoms. More than 75 percent of patients with ovarian cancer are diagnosed after the disease has spread beyond the pelvis. At this late stage, the cure rate is under 15 percent. Therefore, early detection of ovarian cancer is of paramount importance. Current screening uses pelvic examination, a blood test for the cancer antigen CA-125, and transvaginal ultrasound. Even when combined, the sensitivity and specificity of these tests are insufficient for routine screening, as demonstrated in a recent report on the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

OVARIAN CANCER BIOMARKERS

The OCRP has supported the discovery of biomarkers for early ovarian cancer detection. With funding from an FY98 Program Project Award, Dr. Samuel Mok at the Brigham and Women's Hospital identified Ep-CAM and hK6 serum biomarkers when screening women for early signs of ovarian cancer. FY02 Idea Development Award recipient Dr. Honami Naora at the University of Texas M.D. Anderson Cancer Center showed that a set of three HOX genes control the development of each of the three major histological subtypes of epithelial ovarian cancer. Development of new approaches to detect ovarian cancer also holds promise.

ASSESSING THE LEVELS OF LYSOPHOSPHATIDIC ACID IN OVARIAN CANCER

Lysophosphatidic acids (LPAs) are known to be overexpressed in many ovarian cancers and can be detected in blood and ascites. FY02 Idea Development Award recipient Dr. Gordon Mills of M.D. Anderson Cancer Center is developing a high-throughput technology for measuring LPAs that is suitable for ovarian cancer screening. His approach combines the development of specific antibodies to phospholipids and lyso-phospholipids that will bind the more common LPAs in plasma and will detect bound LPAs via surface-enhanced laser desorption and ionization time of flight mass spectroscopy.



NOVEL BIOINFORMATIC TOOLS FOR OVARIAN CANCER

FY04 New Investigator Award recipient Dr. Igor Jurisica of the Ontario Cancer Institute, Princess Margaret Hospital, is creating computational tools and methods for analysis of complex and diverse biochemical, biological, and clinical data on epithelial ovarian cancer by combining publicly available sources of information on antibodies, proteins, the metabolic pathways from the Kyoto Encyclopedia of Genes and Genomes database, ovarian cancer protein array data, single nucleotide polymorphism data, and genomic hybridization databases comparing diverse tumor samples, normal controls, and cell lines. Work thus far has yielded several sets of genes differentially expressed between tumors of different grades and normal ovarian surface epithelial cells, as well as androgen-modulated genes from BRCA mutation carriers. These findings will contribute to the prediction of ovarian cancer outcome and survival. These innovative bioinformatics tools developed by Dr. Jurisica should identify new diagnostic and prognostic markers for epithelial ovarian cancer.

NEW MOLECULAR TECHNOLOGY TO IDENTIFY CANDIDATE OVARIAN CANCER ONCOGENES

A new molecular technology called digital karyotyping was developed by Dr. Tian-Li Wang of Johns Hopkins University Medical School, recipient of an FY04 New Investigator Award. This method allows investigators to analyze DNA copy number alterations on a genome-wide scale with high resolution by extracting and counting sequence tags associated with each locus of the genome. After demonstrating in a pilot study that amplification at chromosome 11q13.5 was associated with carcinomas and the ovarian cancer cell line OVCAR3, Dr. Wang and colleagues examined a set of 211 patient specimens for such amplifications. This analysis identified an amplification associated with high-grade serous carcinoma, and transcriptional analysis of the region identified overexpression of the Rsf-1 gene. Levels of Rsf-1 expression correlate with clinical outcome; overexpression or knockdown of Rsf-1 in vitro shows that it plays a role in ovarian cancer. As shown with the identification of the Rsf-1 gene, digital karyotyping is a powerful technique to identify potential oncogenes and biomarkers of ovarian cancer.





Making an Impact: Development of Preclinical Therapeutics

Most patients with ovarian cancer are diagnosed with late-stage disease when the cancer has spread outside the ovaries. Surgery to remove as much of the tumors as possible (“debulking”) is an important part of treatment, as is systemic, platinum-based chemotherapy. However, several recent Phase 3 trials of combination chemotherapies have had disappointing results, and some researchers and clinicians question how much improvement in standard systemic chemotoxic therapies can be obtained. The OCRP has long recognized this issue and beginning in 2000, made it a priority to fund the preclinical development of new kinds of therapies, including targeted therapies.



LIPOSOME-BASED RADIOTHERAPIES FOR THE TREATMENT OF OVARIAN CANCER



Dr. George Sgouros of Johns Hopkins University received an FY02 Idea Development Award to develop radiation therapies for advanced ovarian cancer. Radionuclides such as actinium-225 emit high-energy alpha particles effective at killing tumor cells. Alpha particles do not penetrate far through tissue so they offer minimal normal tissue irradiation once delivered to metastases. Dr. Sgouros and his team prepared novel multivesicular liposomes (MUVELs) to deliver the parent radionuclide and its daughter particles to tumors. The MUVELs are conjugated with trastuzumab for specific targeting to ovarian cancer cells. Promising results from in vitro studies with the SKOV3 ovarian cancer cell line prompted in vivo studies, which were also successful. While further studies are required to boost the retention of daughter nuclides and reduce organ toxicity, MUVELs show promise for enhancing alpha therapy against advanced metastatic ovarian cancer.

NOVEL PEPTIDES FOR OVARIAN CANCER IMMUNOTHERAPY

Using a patient's own immune system to attack cancer is a promising area of research. Dendritic cells (DCs) play an important role in the immune system by presenting foreign antigens, such as a tumor antigen, to the body's cytotoxic T-cells. The cytotoxic T-cells then destroy the tumor cells. Dr. Alessandro Santin of the University of Arkansas for Medical Sciences, a recipient of an FY02 Idea Development Award, developed DC lines targeted to ovarian cancer tumors. He showed that the serine proteases TADG-12 and CA125/MUC16 are produced in large amounts by ovarian cancer cells but not by normal cells. Therefore, Dr. Santin and colleagues prepared peptide fragments of these proteases to determine and identify which peptide sequences within TADG-12 and CA125/MUC16 can kill a patient's own cancer cells. Data suggest that DCs can induce a cytotoxic T lymphocyte response against specific TADG-12 and CA125/MUC16-derived peptides in patients with ovarian cancer. These results may lead to the development of therapeutic vaccines to prevent disease recurrence or progression for patients with ovarian cancer.



Making an Impact: New Investigators

The OCRP New Investigator Award (NIA) mechanism was designed to attract new researchers into the field of ovarian cancer. The NIA was offered as an individual award mechanism during FY99, FY00, FY03 to FY04, and as part of the Program Project Award during FY98, FY00, and FY01. Eligibility requirements for this mechanism included independent investigators within 6 years of fellowship/postdoctoral positions or investigators established in other fields with less than 3 years experience in ovarian cancer research.

The OCRP conducted an assessment of the NIA mechanism to determine its effectiveness in funding and retaining new researchers in ovarian cancer research and in leveraging research funds. Data from the FY99 to FY00 NIA mechanism and FY98, FY00, and FY01 NIAs supported by the Program Project Awards were examined (see Table V-2). Twelve additional NIAs were supported in FY03 and FY04 (data not analyzed).

Table V-2. Number of Awards and Investment in OCRP New Investigator Awards

Award Mechanism	Fiscal Year	Awards	Investment
NIA	99	16	\$6.86M
	00		
NIA from Program Project Awards	98	9	\$3.86M
	00		
	01		



Of the 25 OCRP-supported new investigators, 18 (72 percent) are still active in ovarian cancer research. The initial \$10.72M investment by the program has resulted in an additional 46 awards totaling \$85.52M in research funding from the DOD, National Institutes of Health, and the American Cancer Society. A total of 41 percent of these subsequent awards was in ovarian cancer research (see Figure V-4). In addition, these investigators have published 359 articles during the past 3–4 years, and of these, 135 are specific to ovarian cancer. A breakdown of these publications by cancer type is shown in Table V-3. Collectively, these analyses show that the NIA mechanism is effective at both attracting and retaining new investigators in ovarian cancer research and leveraging research funds.

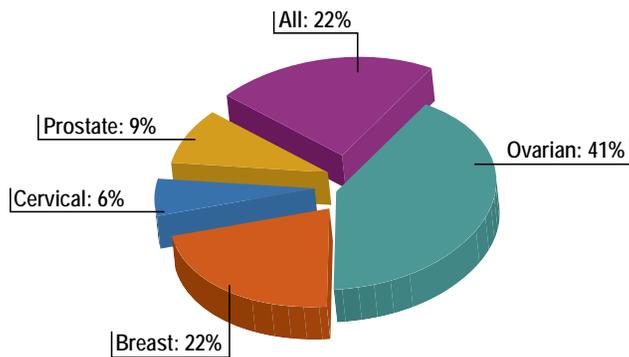


Figure V-4. Percentage of Total Subsequent Awards Received by the OCRP

Table V-3. Subsequent Publications by 25 FY98–FY01 OCRP New Investigator Award Recipients

Type of Cancer	Publications
Ovarian Cancer	135
Breast Cancer	70
Cervical Cancer	8
Uterine Cancer	7
Prostate Cancer	4
Applicable to All Cancers	135
TOTAL	359



Making an Impact: Product-driven Research and Development

The CDMRP has been working together with the Small Business Innovation Research/Small Business Technology Transfer (SBIR/STTR) programs to leverage research and product development not supported elsewhere by the CDMRP. These programs are product driven with the intent that a technology, product, or service will be developed that the government potentially can use and that the small business or research institution can commercialize outside of the SBIR/STTR programs. Highlights of three promising SBIR/STTR projects that are impacting ovarian cancer detection and treatment follow.

BIOMAGNETIC IMAGING AND TREATMENT OF OVARIAN CANCER USING MAGNETIC NANOPARTICLES

Senior Scientific Inc., is developing a novel technology that can examine a patient rapidly for the presence of ovarian cancer and localize the cancer site for treatment. The technology uses biomagnetic sensors (magnetic particles linked to specific antibodies recognizing ovarian cancer cells and angiogenesis agents) that bind to precancerous or early ovarian cancer lesions. The lesions then would be detected by imaging with Superconducting Quantum Interference Detector magnetic sensors. Studies are under way to examine the use of these particles for targeted drug delivery.

NANOPARTICLE SELF-LIGHTING PHOTODYNAMIC THERAPY FOR OVARIAN CANCER

Nomadics is creating a new efficient treatment modality for cancer by combining radiotherapy and photodynamic therapy (PDT), which may be more effective, economical, simpler, and convenient than conventional PDT. The company has designed and synthesized scintillation nanoparticles with strong self-luminescence. Self-luminescence will be a critical component of this therapy, especially for the treatment of ovarian cancer, as to date it has not been possible to excite nanoparticles externally at a distance from the skin to the ovaries. Preliminary data indicate that this therapy is a promising modality for cancer treatment.

NANOCAPSULES FOR OVARIAN CANCER GENE THERAPY

Transgenex Nanobiotech Inc., is developing an advanced technology for the targeted treatment of ovarian cancer using the vertebrate Sleeping Beauty Transposon DNA system. Sleeping Beauty is a nonviral gene transfer system that can insert new genes into vertebrate genomes more effectively than any transposon available today. In this project, the gene delivered will be for the atrial natriuretic peptide NP73-102, whose overexpression has been shown to induce apoptosis. If long-term expression of the inserted gene can be achieved, it should kill the ovarian tumor cells in which it is expressed. This technology has a potential application not only for the treatment of ovarian cancer but may have broad application for other cancers and for infectious diseases.



