

# *Section VI.*

# *OVARIAN CANCER*

# *RESEARCH*

# *PROGRAM*



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# Ovarian Cancer Research Program

**Vision:** To prevent ovarian cancer.

**Mission:** To support innovative, integrated, multidisciplinary research efforts that will lead to a better understanding, control, and prevention of ovarian cancer.

## **Congressional Appropriations for Peer Reviewed Research**

\$27.5M in FY97–99, \$12M in FY00, and \$12M in FY01

## **Award Summary**

26 awards from the appropriations FY97–99

14 awards from the FY00 appropriation

~5 awards anticipated from the FY01 appropriation

## The Disease

*“The post-genomic age offers extraordinary opportunities to learn more about the biology of ovarian cancer, which will ultimately lead to new preventive and therapeutic strategies. The OCRP is playing a vital role in bringing these opportunities to fruition through its unparalleled commitment to funding innovative, discovery-driven, high-risk research.”*

—Brad Nelson, Ph.D.,  
Affiliate Assistant Professor,  
Virginia Mason Research  
Center  
OCRP Award Recipient



Ovarian cancer is projected to be the fifth most common cause of cancer death among women in the United States in 2001. This year an estimated 23,400 women will be diagnosed with and 13,900 will die from ovarian cancer in the United States. Among gynecological cancers in 2001, ovarian cancer ranks second in the number of new cases and first in the number of cancer deaths.<sup>1</sup> There is no routine screening test for ovarian cancer, a disease that is often without overt or specific symptoms until late in the disease process. Early diagnosis is important because women with localized ovarian cancer have a better chance of being cured. Yet, only 25% of ovarian cancer cases are diagnosed with localized (early stage) disease. We are only beginning to understand the biology and etiology of ovarian cancer to develop better prevention, screening, and therapeutic approaches to this deadly disease.

## History of the Ovarian Cancer Research Program

### —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. At that time, the U.S. Army Medical Research and Materiel Command convened a meeting of expert scientists, clinicians, and consumer advocates in the field of ovarian cancer to define the goals and areas of emphasis of the program. Participants were drawn from academia, oncology societies and

<sup>1</sup> American Cancer Society – *Cancer Facts and Figures 2001*.

associations, consumer advocacy organizations, military, and cancer research funding agencies to identify underrepresented avenues of research and novel applications of existing technologies and to avoid duplicative research efforts. The overall mission of the DOD OCRP is to support innovative research efforts leading to a better understanding, control, and prevention of ovarian cancer. The key initiatives of the OCRP are building infrastructure and supporting innovative research that will foster new directions for, address neglected issues in, and bring new independent investigators into the ovarian cancer field.

*“Ovarian cancer has been a significant public health problem. However, exciting discoveries in the laboratory hold great potential for leading to effective methods for prevention and treatment of the disease. The funding opportunities provided by the Department of Defense are making a tremendous impact in advancing ovarian cancer research forward.”*

—Gustavo Rodriguez, M.D.  
Associate Professor, Duke University  
Medical Center  
OCRP Award Recipient



**—Congressional Appropriation and Funding History**

From FY97–01, Congress appropriated a total of \$51.5M to fund peer reviewed ovarian cancer research through the OCRP. A total of 40 awards have been made in three award mechanisms: Program Project Awards, Idea Awards, and New Investigator Awards. Each fiscal year’s investment strategy focuses on the program’s vision to prevent ovarian cancer. Appendix B, Table B–4, summarizes congressional appropriations and the investment strategy executed by the OCRP for FY00–01. Additional details of the FY97–99 programs may be found in the *DOD Congressionally Directed Medical Research Program Annual Reports* of September 1999 and of September 2000.

**FY00 Program**

Congress appropriated \$12M in FY00 to continue the peer reviewed DOD OCRP. The key initiatives of the program were to prepare new independent investigators for careers in ovarian cancer research, attract more senior investigators new to the ovarian cancer field, and build research infrastructure. To accomplish these initiatives, the programmatic vision was implemented by offering two award mechanisms, New Investigator Awards and Program Projects. Table VI–1 provides a summary of the FY00 OCRP award mechanisms. As illustrated in Figure VI–1, the portfolio of research supported by the FY00 OCRP is diverse.

**Table VI–1. Funding Summary for FY00 OCRP**

<b>Award Mechanism</b>	<b>Number of Proposals Received</b>	<b>Number of Awards</b>	<b>Investment</b>
New Investigator Awards	112	10	\$4.5M
Program Project Awards	11	3	\$5.0M
Other-Investigator Initiated Awards <sup>1</sup>	N/A	1	\$0.5M
<b>Total</b>	<b>123</b>	<b>14</b>	<b>\$10.0M</b>

<sup>1</sup> In FY00, one individual research project that was submitted as part of a Program Project was recommended for funding during programmatic review.

*“Ovarian cancer is the fifth leading cause of cancer death in women in the United States. The focus of the DOD OCRP has been to use the limited funds available to develop research infrastructure and bring new investigators into this important area of research. This is a vital research program for women’s health and the management of this program by the DOD is outstanding.”*

—William Hoskins, M.D.  
Avon Chair of Gynecologic  
Oncology Research, Memorial  
Sloan-Kettering Cancer Center  
FY01 OCRP Integration  
Panel Chair



*Ovarian cancer is often not associated with any obvious signs or symptoms until late in its development. Signs and symptoms of ovarian cancer may include:*

- *General abdominal discomfort and/or pain (gas, indigestion, pressure, swelling, bloating, cramps)*
- *Nausea, diarrhea, constipation, or frequent urination*
- *Loss of appetite*
- *Feeling of fullness even after a light meal*
- *Weight gain or loss with no known reason*
- *Abnormal bleeding from the vagina*

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

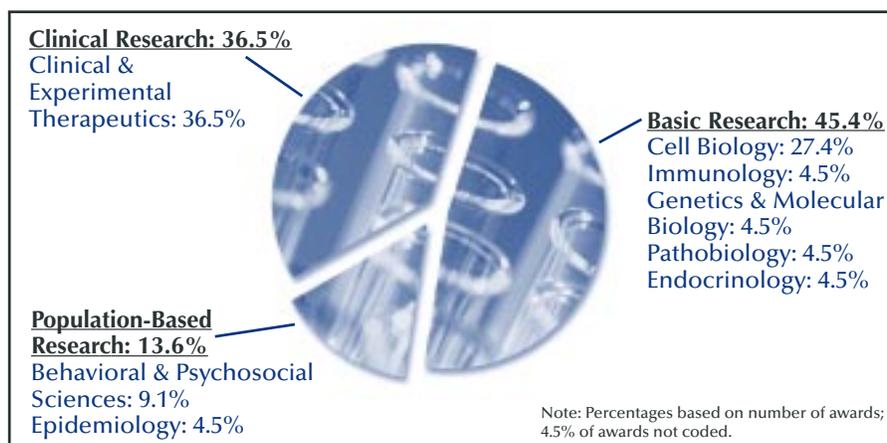


Figure VI-1. FY00 OCRP Portfolio by Research Area

## FY01 Program

Congress continued the OCRP with a \$12M appropriation in FY01, thus marking the start of the fifth fiscal year for the OCRP. The FY01 programmatic vision focused on building research infrastructure through the continuation of Program Project Awards. These awards will also support innovative research ideas and new ovarian cancer researchers, as either an Idea or New Investigator project was required to be part of a Program Project submission. In addition to continuing to emphasize research in the areas of etiology, early detection/diagnosis, preclinical therapeutics, and quality of life, applicants were also encouraged to submit in the areas of prevention and behavioral studies. In response to the FY01 OCRP Program Announcement, 29 proposals were received in July 2001. Scientific peer review and programmatic review are scheduled for October 2001 and January 2002, respectively. Approximately five Program Project Awards are anticipated.

## Scientific Achievements

The eight awards made in the first 2 years of the program enhanced ovarian cancer research infrastructure by the establishment of new centers that focus on this disease (Figure VI-2). The success of OCRP-funded research can be gauged, in part, by the number of resultant publications, abstracts/presentations, and patents/licensures reported by awardees. This information is summarized in Table VI-2.

Table VI-2. FY97-98 OCRP Award Outcomes

Number of Awards	8
Publications in Scientific Journals	>10
Abstracts/Presentations at Professional Meetings	>50

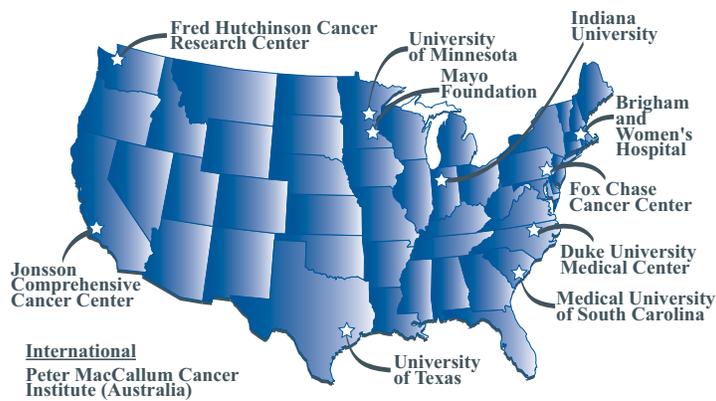


Figure VI-2. FY97-98 OCRP Program Project Awards Distribution

Five of the eight Program Projects funded in FY97-98 are described below. These represent some of the most exciting advances in ovarian cancer research already made in the first 3 years of the program.

**Antibody Immunity to Cancer-Related Proteins as a Serologic Marker for Ovarian Cancer. Brad Nelson, Ph.D., Virginia Mason Research Center:** Present methods of ovarian cancer screening suffer from limited sensitivity and specificity. For example, ultrasound and CA-125, a serological marker of ovarian cancer, can only reliably detect advanced disease. Thus, the need for an improved ovarian cancer screening test that readily detects early-stage disease is evident. OCRP-supported investigators at the Fred Hutchinson Cancer Center, in collaboration with the University of Washington and Virginia Mason Research Center, are trying to determine whether the presence of antibodies to specific ovarian cancer proteins can be used as reliable indicators of early-stage ovarian cancer. Prior work has identified three different tumor antigens that cause antibodies to be produced in the blood of women with ovarian or other cancers. These proteins are named HER2/neu, p53, and Myc. Blood from women without cancer, women with benign ovarian masses, and women with ovarian cancer are being tested to see if the presence of these three and other antibodies to these proteins distinguishes women with cancer from those without. To date, 19 proteins have been identified that in preliminary studies appear to induce antibody responses exclusively in patients with ovarian cancer. In addition to their potential utility for early detection of ovarian cancer, a subset of these proteins shows promise as a target for immune-based therapy of ovarian cancer such as cancer vaccines.

*“Thousands of women and their families are afflicted by the burden of ovarian cancer. Over the past decade, the Department of Defense OCRP has led the charge to help these patients by clarifying the biology of ovarian cancer, by identifying new ovarian cancer prevention strategies, and by developing novel therapeutics for the treatment of ovarian cancer. The Department of Defense OCRP should be congratulated for taking on this honorable task.”*

—Ronald Alvarez, M.D.  
Professor and Ellen Gregg Shook  
Culverhouse Chair, University of  
Alabama at Birmingham  
Integration Panel Executive Committee  
Member



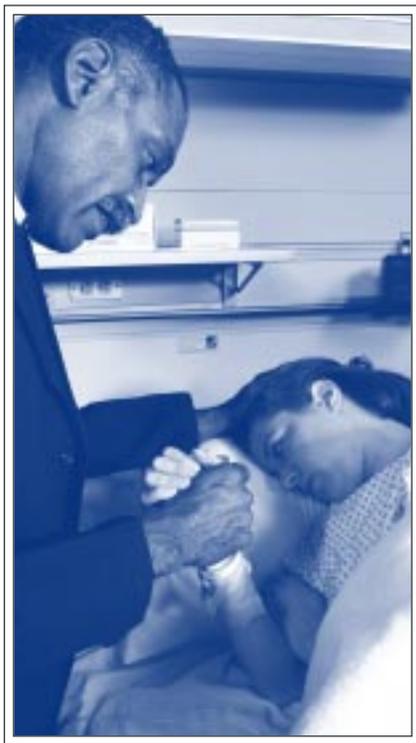
*“Through its Ovarian Cancer Research Program, the Department of Defense is funding cutting edge research aimed at advancing knowledge about the etiology, early detection and prevention of ovarian cancer. These new insights will help us eliminate the fear and trepidation currently associated with the diagnosis of ovarian cancer.”*

*—Beth Karlan, M.D.*

*Director, Division of Gynecologic Oncology and the Gilda Radner Ovarian Cancer Program  
FY01 OCRP Integration Panel  
Chair-Elect*

***Chemoprevention of Ovarian Cancer with Progestin. Gustavo Rodriguez, M.D., Duke University Medical Center:*** For a number of years, clinicians have attempted to understand the association between oral contraceptive use and subsequent lower ovarian cancer risk. While various theories help explain the nature of this association, the actual underlying mechanism behind this protective effect of oral contraceptives largely remains unknown. If this mechanism can be elucidated, it may be possible to devise a chemopreventive strategy that is more effective than oral contraceptives while not interfering with ovulation or causing other side effects. In preliminary laboratory studies, OCRP-funded researchers have demonstrated that the progestin component of oral contraceptives activates cancer preventive molecular pathways in the ovary, suggesting that a strong biologic effect independent of ovulation may underlie the protective effect of oral contraceptives against ovarian cancer. In a primate model comparing the combined and individual components of a common oral contraceptive product to a control, the group of monkeys that received progestin demonstrated significantly greater programmed cell death and differential regulation of transforming growth factor-beta in the ovarian surface epithelium. Investigators now hope to determine what known regulators of programmed cell death are affected by progestin and test their hypothesis in domestic fowl, which have a high incidence of spontaneous ovarian cancer, and human cell lines. The long-term plan is to conduct a clinical trial in women at high risk for ovarian cancer.

***Facilitating Decision-Making about Prophylactic Oophorectomy. Suzanne M. Miller, Ph.D., Fox Chase Cancer Center:*** Women with a family history of ovarian cancer are at especially high risk of developing the disease. Since the efficacy of available detection regimens is limited, prophylactic oophorectomy (i.e., surgical removal of healthy ovaries) has emerged as a preventive option for these individuals. Yet, few data are available on how to help women process and make decisions about undergoing prophylactic surgery. OCRP-funded investigators are conducting a study focusing on how women with a familial risk of ovarian cancer make decisions regarding preventive options, specifically prophylactic oophorectomy. The primary goal of the study is to explore the psychological factors that influence a woman’s decision to undergo or forego the procedure. A secondary goal is to identify whether high monitors (i.e., women who typically scan for and exaggerate cancer threats) show a different pattern of response to the decision-making process than low monitors (i.e., women who typically distract from and minimize health threats). Data from preliminary studies reveal that cognitive and affective factors can impact decision making. Through a more systematic investigation of these factors, investigators will be able to develop a profile of decision making that will be used to develop an enhanced counseling intervention. The counseling intervention will be designed to enable the prophylactic oophorectomy candidate to realistically anticipate scenarios that might develop, thereby providing a more informed basis for making a decision and dealing with the consequences. A pilot study will be designed and conducted to provide a preliminary evaluation of the feasibility and efficacy of the counseling intervention.



Research findings emanating from this work will allow women at high risk for developing ovarian cancer to make more informed decisions concerning their health options.

***Regulation of Telomerase Activity in Ovarian Cancer. Patricia A. Kruk, Ph.D., University of South Florida:*** New Investigator Awards are designed to attract new, independent investigators into the ovarian cancer research field. A New Investigator Award has led to identification of a genetic abnormality associated with hereditary ovarian cancer. This abnormality was found in the ovarian surface epithelium (OSE), a single layer of cells enveloping the ovary. The OSE in these women demonstrated premature shortening at the ends of their chromosomes, regions referred to as telomeres. Such premature telomeric shortening causes chromosomal instability. The premise of this study is that increased telomeric instability may contribute to the malignant transformation of OSE. To test this hypothesis, an ovarian culture model system has been developed in which telomerase activity can be controlled in both normal and cancerous ovarian cells. The immediate goal of this study is to use this system to determine the molecular mechanisms that regulate telomerase activity in ovarian cancer. The long-term goals of this study are to evaluate the effectiveness of telomerase as a potential anti-ovarian cancer target, and to design novel therapeutic modalities specifically targeted to ovarian cancer.

***Development of a Novel Vaccine with Fusions of Dendritic and Ovarian Cancer Cells from Patients. Jianlin Gong, M.D., Harvard Medical School:*** Idea Awards represent innovative approaches to ovarian cancer research. An Idea Award to the Dana-Farber Cancer Institute involves the pursuit of a novel approach



### ***Building Infrastructure***

In the first year of the OCRP, the Integration Panel was faced with the challenge of how to best provide additional foundations for ovarian cancer research. An investment strategy was developed that would build infrastructure via the Program Project Award mechanism. The success of the early Program Projects led to the continuation of this award mechanism in FY98, FY00, and FY01. These 11 awards (Figure VI-2) have brought together experts from multiple disciplines. Through their synergistic research projects integrated around one or more emphasis areas, they are stimulating ovarian cancer and/or primary peritoneal carcinoma research. FY97-98 investigators have disseminated their research results and presented their latest research advances by publishing their work in prestigious science journals and presenting over 30 abstracts/presentations at national and international forums. The establishment of 12 core facilities (e.g., cell and tissue repositories and laboratory core facilities) provides resources that will sustain future biomedical research in ovarian cancer. Moreover, the M.D. Anderson Cancer Center, Fred Hutchinson Cancer Research Center, and Fox Chase Cancer Center were awarded National Cancer Institute Specialized Program of Research Excellence grants to support translational research approaches that may have an immediate impact on improving ovarian cancer care and prevention. ♦

*“One of the many exciting characteristics of the OCRP is its flexibility and responsiveness to the ovarian cancer community. This past year, the Program Announcement reflected advice from consumers and behavioral scientists regarding the need to include behavioral studies as an additional emphasis area.”*

—Steven Krosnick, M.D.  
OCRP Manager

to ovarian cancer vaccine development. The research strategy involves the fusion of human dendritic cells (i.e., cells that present a substance or “antigen” to immune system cells in such a way that it is recognized as a threat) with ovarian cancer cells to generate effective antitumor immunity in patients. In the ongoing study, ovarian carcinoma cells derived from patients were successfully fused with autologous dendritic cells. The created fusion cells expressed tumor-associated antigens, such as CA-125, HER2/neu, and MUC1, and DC-derived co-stimulatory and adhesion molecules. The fusion cells were functional in stimulating the proliferation of autologous T cells. Significantly, the T cells derived from patients with ovarian cancer were stimulated by the fusion cells to kill the autologous ovarian tumor cells. These findings demonstrate that fusions of human ovarian cancer cells with autologous DC induce specific cytotoxicity T cells against autologous ovarian cancer cells, and thus have the potential to serve as a tumor vaccine.

## Summary

Since 1997, the DOD OCRP has been responsible for managing \$51.5M in congressional appropriations, which has resulted in 40 awards for FY97–00. The OCRP is building infrastructure and supporting innovative research. This program has supported a diverse multidisciplinary portfolio that encompasses etiology, prevention, early detection/diagnosis, preclinical therapeutics, quality of life, and behavioral research projects. OCRP investigators have intensified the fight against ovarian cancer and are aiding in the national health effort that will impact the well-being of women.

## FY01 Integration Panel Members

**Chair, William Hoskins, M.D.:** Deputy Physician-in-Chief, Disease Management; Chief, Gynecology Service, Department of Surgery; and Avon Chair of Gynecologic Oncology Research, Memorial Sloan-Kettering Cancer Center. Professor, Department of Obstetrics and Gynecology, Cornell University Weill Medical College.

**Chair-Elect, Beth Karlan, M.D.:** Director, Division of Gynecologic Oncology and the Gilda Radner Ovarian Cancer Program, Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center. Associate Professor, Department of Obstetrics and Gynecology, University of California, Los Angeles.

**Chair Emeritus, Michael Birrer, M.D., Ph.D.:** Chief, Molecular Mechanisms Section, Department of Cell and Cancer Biology, Division of Clinical Sciences, National Cancer Institute, National Institutes of Health. Assistant Professor, Uniformed Services University of the Health Sciences.

**Ronald Alvarez, M.D.:** Professor and Ellen Gregg Shook Culverhouse Chair, Division of Gynecologic Oncology; and Scientist, Comprehensive Cancer Center, University of Alabama at Birmingham.



**Debra Bell, M.D.:** Associate Pathologist, Massachusetts General Hospital; Associate Professor of Pathology, Harvard Medical School.

**Holly Gallion, M.D.:** Professor, Department of Obstetrics, Gynecology and Reproductive Sciences; Director, Ovarian Cancer Center of Excellence of the University of Pittsburgh Medical Center Health System, Magee-Women's Research Institute, and University of Pittsburgh Cancer Center.

**David Gershenson, M.D.:** Director, Blanton-Davis Ovarian Cancer Research Program; Ann Rife Cox Chair in Gynecology; and Professor and Chair, Department of Gynecologic Oncology, The University of Texas M.D. Anderson Cancer Center.

**Thomas Hamilton, Ph.D.:** Senior Member, Department of Medical Oncology, and Leader, Ovarian Cancer Program, Fox Chase Cancer Center. Adjunct Professor, Department of Chemistry, Lehigh University.

**Enrique Hernandez, M.D.:** Director, Division of Gynecologic Oncology, and Professor of Obstetrics and Gynecology and of Pathology, Temple University School of Medicine.

**Hedvig Hricak, M.D., Ph.D.:** Chairman, Department of Radiology, Memorial Sloan-Kettering Cancer Center. Carroll and Milton Petrie Chair, and Professor of Radiology, Cornell University.

**Ann Kolker, J.D.:** Consumer, Executive Director, Ovarian Cancer National Alliance.

**Maurie Markman, M.D.:** Director, Cleveland Clinic Taussig Cancer Center. Chairman, Department of Hematology/Medical Oncology, and The Lee and Jerome Burkons Research Chair in Oncology, The Cleveland Clinic Foundation.

**Geraldine Padilla, Ph.D.:** Vice-President, Cancer Control, American Cancer Society California Division.

**Harvey Risch, M.D., Ph.D.:** Associate Professor of Epidemiology and Public Health, Yale University School of Medicine.

**Elwood Robinson, Ph.D.:** Professor and Chair, Department of Psychology, North Carolina Central University.

**Mary Scroggins, M.A.:** Consumer, Member of the Board of Directors of the Ovarian Cancer National Alliance. Founder and publisher of *SisterCircle* newsletter.

**Michael Steller, M.D.:** Director of Research, Program in Women's Oncology, Women and Infants' Hospital; Associate Professor, Department of Obstetrics and Gynecology, Brown University School of Medicine.

**Robert Young, M.D.:** President, Fox Chase Cancer Center. Year 2001 President-Elect of the American Cancer Society.

*“Having served on both the Scientific Peer Review Panel and the Integration Panel as a consumer member, I am impressed by the integrity and thoroughness of the program design and heartened by the progress made possible through DOD OCRP-funded research. Women and their families, health care providers, and others involved in this important area of research are indebted to this unique program, which assembles consumers, scientists, and clinicians as equal partners in setting the pace for ovarian cancer research and in improving survival—both qualitatively and quantitatively.”*

*—Mary Scroggins  
Board of Directors, Ovarian Cancer National Alliance  
Integration Panel Member  
and Peer Reviewer*

❖ *For more information about the OCRP and other programs managed by the CDMRP, visit <http://cdmrp.army.mil>* ❖