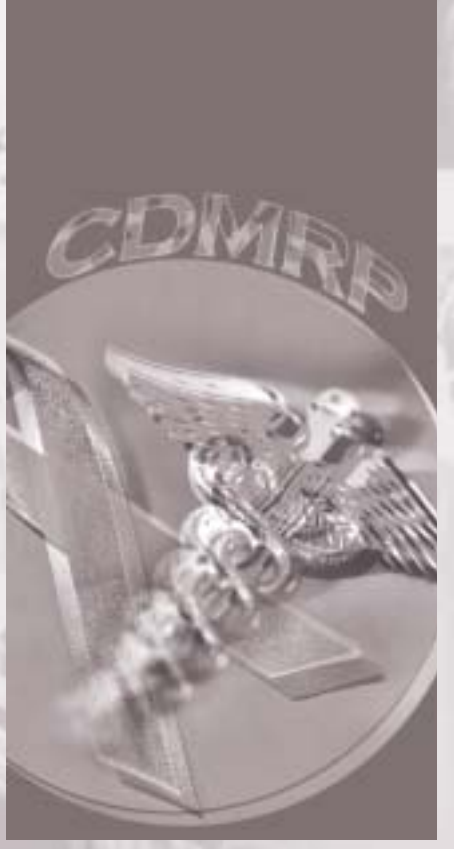


Section VI
Ovarian Cancer Research Program

Vision: To eliminate ovarian cancer.

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

Congressional Appropriations for Peer-Reviewed Research: $39.5M in FY97–00, $12M in FY01, and $10.2M in FY02

Funding Summary: 40 awards from the FY97–00 appropriations; 5 awards from the FY01 appropriation; ~20 awards anticipated from the FY02 appropriation

The Disease

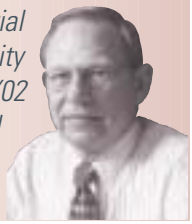
Ovarian cancer ranks second among gynecological cancers in the number of new cases, and first among gynecological cancers in the number of deaths each year. In 2002, approximately 23,300 women will be diagnosed with ovarian cancer in the United States alone, and 13,900 will die from the disease. Ovarian cancer is often without overt or specific symptoms until late in its development; therefore, most women are diagnosed with advanced stage disease. As a result, women diagnosed with ovarian cancer have a 5-year survival rate of only approximately 50%. However, local ovarian cancer has a 95% 5-year relative survival rate, thus emphasizing the need for early diagnosis.[1]

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 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, integrated, multidisciplinary research efforts that will lead to a better understanding, detection, diagnosis, prevention, and control 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.

"One of the most important accomplishments of the OCRP has been the development of new academic sites with research infrastructure and the attraction of new investigators into ovarian cancer research. Many of the OCRP grant recipients have gone on to get independent NCI funding (RO1, PO1 or SPORE)."

—William Hoskins, M.D., Director, Curtis and Elizabeth Anderson Cancer Institute, Memorial Health University Medical Center, FY02 Integration Panel Chair-Emeritus



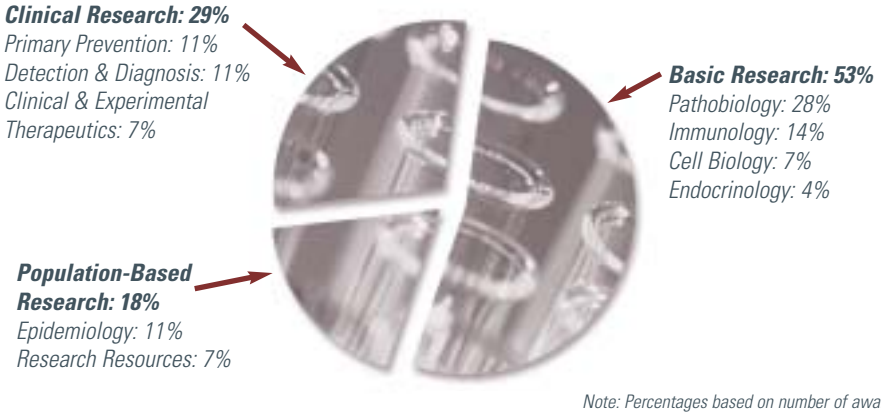
From FY97–02, Congress appropriated a total of $61.7M to fund peer-reviewed ovarian cancer research through the OCRP. A total of 45 awards have been made through FY01 in four award mechanisms: Program Project, Idea, Investigator-Initiated, and New Investigator Awards. Each fiscal year's investment strategy focuses on the program's vision to eliminate ovarian cancer. Appendix B, Table B-4, summarizes congressional appropriations and the investment strategy executed by the OCRP for FY01–02. Additional details of the FY97–00 programs may be found in the DOD Congressionally Directed Medical Research Programs Annual Reports of September 1999, September 2000, and September 2001.

[1] *American Cancer Society - Cancer Facts and Figures 2002.*

FY01 PROGRAM

Congress appropriated $12M in FY01 to continue the peer-reviewed DOD OCRP, marking the fifth fiscal year for this program. 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. For additional details on the components of a Program Project Award, refer to the box story on page VI-4.

In addition to emphasizing 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. Table VI-1 provides a summary of the FY01 OCRP award categories and mechanisms in terms of number of proposals received, number of awards, and dollars invested. As illustrated in Figure VI-1, the portfolio of research supported by the FY01 OCRP is diverse.



Note: Percentages based on number of awards.

Figure VI-1. FY01 OCRP Portfolio by Research Area

THE VISION FOR THE FY02 PROGRAM

Congress continued the OCRP with a $10.2M appropriation in FY02 for peer-reviewed ovarian cancer research. The OCRP is offering two new award mechanisms: Idea Development Awards and Institutional Training Grants.

- Idea Development Awards are designed to encourage innovative approaches to ovarian cancer research. Idea Development Award proposals are intended to stimulate and reward innovative research ideas that may be viewed as high risk but have the potential for high gain in scientific and clinical knowledge.
- Institutional Training Grants are intended to encourage the initiation of new postgraduate training programs in ovarian cancer. These awards should draw postdoctoral students focused on ovarian cancer research together in a common research and training environment.

In response to the FY02 OCRP Program Announcement, 201 proposals were received electronically, as detailed in Table VI-2. Scientific peer review was conducted in August 2002, and programmatic review is scheduled for November 2002. Approximately 20 awards are anticipated.

"The DOD OCRP is supporting some of the most important research in ovarian cancer being done in this country today."
—Stephen Rubin, M.D., Director, Division of Gynecologic Oncology, The University of Pennsylvania Medical Center, FY02 Integration Panel Member

Table VI-1. Funding Summary for the FY01 OCRP

Category and Award Mechanism	Number of Proposals Received	Number of Awards	Investment
Infrastructure			
Program Project	*29*	*5*	*$10.3M*

The Essence of an OCRP Program Project

In the first year of the OCRP, Program Project Awards were offered in an effort to build infrastructure in the field of ovarian cancer research. Due to the success of this award, coupled with the continuing need to build the necessary infrastructure to support ovarian cancer research, Program Project Awards have been offered through 4 program cycles. A total of 16 Program Project Awards have been made, and the establishment of these centers has led to new collaborations across research disciplines and institutions. The intent of these awards has continued to focus on supporting innovative research and attracting new independent investigators into the ovarian cancer research field.

Program Project Awards must include multiple research projects and at least one core facility. To facilitate innovative research and new investigators, the OCRP required that research projects incorporate one or both of these themes. For example, in FY01, one of the research projects had to be an Idea or New Investigator Research Project, as defined below:

- *Idea Research Projects are intended to stimulate and reward creative ideas that may be viewed as speculative, but with the potential for high payoff.*
- *The intent of New Investigator Research Projects is to encourage new investigators to pursue research in the field of ovarian cancer.*

These awards are providing resources that will sustain future biomedical research in ovarian cancer across the country (Figure VI-2).

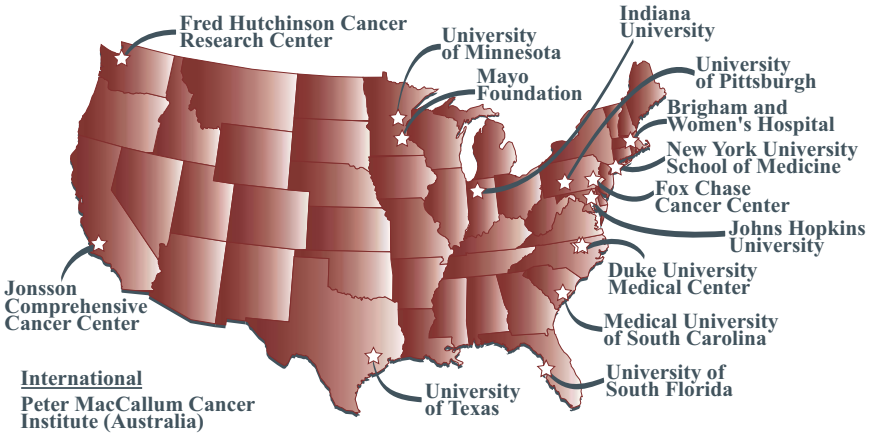


Figure VI-2. OCRP Program Project Awards Distribution

Table VI-2. Award Mechanisms Offered and Proposals Received for the FY02 OCRP

Category and Award Mechanism	*Number of Proposals Received*
Research	
Idea Development	*196*
Training/Recruitment	
Institutional Training Grants	*5*
Total	***201***

Scientific Outcomes and Advances

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-3.

The following highlights represent some of the most exciting advances in ovarian cancer research supported by the DOD OCRP. These examples represent the research of dedicated investigators working to support the program's vision of eliminating ovarian cancer.

Biological Basis for Chemoprevention of Ovarian Cancer.

Andrew Berchuck, M.D., Duke University Medical Center: Ovarian cancer is not often detected until it reaches advance stages. Survival significantly improves if the cancer is detected early. Unfortunately, methods for the early detection of ovarian cancer are lacking. The location of the ovaries makes physical examination an ineffective means of detection, and screening techniques such as CA125 blood test and transvaginal ultrasound are costly and often inaccurate. OCRP award recipients at Duke University are studying the value of symptom recognition as an important way to detect ovarian cancer. Symptoms of ovarian cancer often resemble those of other common diseases and include abdominal discomfort, increased urinary urgency or

"Support provided by OCRP has funded critically important research in the etiology, prevention, and treatment of ovarian cancer, a disease that is generally associated with poor overall survival. Thousands of women stand to potentially reduce their risk of ovarian cancer and improve their outcome if diagnosed with ovarian cancer by virtue of the progress being made in OCRP-sponsored research. The importance of this contribution to women's health cannot be understated."

—Ronald Alvarez, M.D., Ellen Gregg Shook Culverhouse Chair in Gynecological Oncology, University of Alabama at Birmingham, Integration Panel Executive Committee Member-at-Large

frequency, and irregular menstrual bleeding. A recent study conducted by investigators at Duke University and their colleagues at the University of Pittsburg confirmed the importance for a greater awareness of symptoms by both patients and physicians.[1] The study evaluated 767 women between the ages of 20 and 69 diagnosed with invasive (n=616) and borderline (n=151) epithelial ovarian tumors from 1994 to 1998. Epidemiological characteristics of patients with either tumor type are similar. The primary goal of this study was to compare types and duration of symptoms prior to diagnosis of invasive or borderline ovarian tumor. Patients with either type of tumor reported similar symptoms. However, patients with borderline tumors were less likely to report symptoms. Patients with borderline tumors also had symptoms for a longer time prior to diagnosis. Borderline cases were more likely to be detected through a routine examine while invasive cases were more likely to be diagnosed because of symptoms. The most dramatic conclusion from this study was that women eventually diagnosed with ovarian cancer had symptoms for 4 months prior to the diagnosis. This study emphasizes the need for more effective screening and prevention strategies aimed at increasing awareness of ovarian cancer symptoms.

[1]Vine MF, Ness R, Calingaert B, Schlidkraut JM, Berchuck A. 2001. Types and duration of symptoms prior to diagnosis of invasive or borderline ovarian tumor. Gynecologic Oncology 83:166-471

Genetic Definition and Phenotypic Determinates of Ovarian Cancer.

Beth Karlan, M.D., University of California Los Angeles: The goal of this OCRP-supported study is to identify biochemical markers that may used to follow the progression of ovarian cancer. It has been shown that enzymes that breakdown the extracellular matrix and basement membrane, structures that normally hold cells in place, participate in invasion and metastases of solid tumors. Investigators at University of California Los Angeles have discovered that one of these enzymes, known as urokinase-type plasminogen activator (uPA), is clearly associated with disease progression and poor prognosis in ovarian cancer.[1] This study was the first to evaluate the prognostic significance of uPA in ovarian cancer through a comprehensive statistical analysis of ovarian cancer samples representative of all stages. Invasive tumors had higher uPA concentrations than low malignant potential tumors. Metastatic lesions and advance stage tumors also had markedly elevated uPA concentrations. These findings all point to a clear association of uPA in malignant progression of epithelial ovarian cancer and support the concept that uPA is an active participant in the mechanism that leads to invasiveness and metastasis of ovarian cancer. Thus, the assessment of uPA concentrations may prove useful to identify ovarian patients at high risk.

[1]Konecny G, Untch M, Pihan A, et al. 2001. Association of urokinase-type plasminogen activator and its inhibitor with disease progression and prognosis in ovarian cancer. Clinical Cancer Research 7:1743-1749.

Table VI-3. FY97-99 OCRP Award Outcomes

Number of Awards	***26***
Publications in Scientific Journals	***>55***
Abstracts/Presentations at Professional Meetings	***>90***
Patents/Licensures (including applications)	***2***

Telomerase-Independent Telomere Maintenance in Ovarian Cancer: A Molecular Genetic Analysis.

Dominque Broccoli, Ph.D., Fox Chase Cancer Center: Ovarian cancer predominantly develops from the malignant transformation of cells on the surface of the ovary or surface epithelium. However, the biological mechanisms leading to transformation remain unclear. Normal cells eventually stop dividing and become senescent. However, in transformed cells, the biochemical machinery that normally stops cell division malfunctions and tumors form. A common genetic change tightly linked to a cell's ability to divide indefinitely occurs at telomeres, structures at the ends of chromosomes. In normal cells, telomeres shorten with each division. After several divisions, the shortened telomeres signal the cell to stop dividing. However, most tumors have telomeres with a stable length and continue to divide indefinitely. Typically, an enzyme known as telomerase is responsible for maintaining telomere length. However, some cells have developed another mechanism for maintaining telomere length called alternative lengthening of telomeres (ALT). At least 30% of ovarian adenocarcinomas are telomerase negative. The significance of this finding lies in its impact on therapeutic drug development, as telomerase inhibitors that are currently under development may not be effective on tumors expressing ALT. Dr. Broccoli and collaborators at Fox Chase Cancer Center are studying human ovarian surface epithelial cell lines that display the ALT pathway for telomere maintenance, to identify genes that are either overexpressed or underrepresented.

These studies are anticipated to improve the prevention, diagnosis, and/or treatment of ovarian cancer.

New Anti-Metastatic and Anti-Angiogenic Compound for Ovarian Cancer.

Erkki Ruoslahti, M.D., Ph.D, The Burnham Institute: In recent years exciting novel therapeutic agents aimed at preventing new blood vessel formation (angiogenesis) in tumors have received considerable attention. Most notable among these agents are the compounds angiostatin and endostatin. These compounds represent a growing class of antiangiogenic agents that are derived from extracellular matrix (ECM) and blood proteins. The ECM that surrounds cells in tissue is important for regulating many cellular functions such as growth, migration, differentiation, and survival. Transformed or malignant cells are less confined by the ECM and consequently tumors arise. OCRP-supported investigators at the Burnham Institute have been working to devise compounds that restore ECM control of malignant cells. To do so, they created superfibronectin, a polymer of fibronectin prepared by mixing fibronectin and anastellin. Anastellin is a 76 amino acid peptide derived from fibronectin that was discovered and named by these researchers. Both superfibronectin and anastellin were shown to be potent inhibitors of tumor growth, angiogenesis, and metastasis in mice.[1] They also showed that when anastellin was combined with fibrinogen, an abundant serum protein involved in blood clotting, it polymerized to form a superfibrinogen. Superfibrinogen has antitumor activity that is similar to superfibronectin and anastellin. Thus, these investigators have identified three new agents with potential therapeutic utility for treatment of ovarian cancer. The fact that

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.

these agents work following systemic rather than local administration may offer an additional advantage for treating ovarian cancer.

[1]Yi M, Ruoslahti E. 2001. A fibronectin fragment inhibits tumor growth, angiogenesis, and metastasis. Proceedings of the National Academy of Sciences 98:620-624.

Role of Oocyte Loss in Ovarian Surface Mesothelial Cell Transformation.

Jonathan Tilly, Ph.D. and Grant McGregor, Ph.D., Massachusetts General Hospital and Emory University School of Medicine: These investigators are exploring a possible cause of ovarian cancer that links the rapid loss of oocytes to increased ovarian surface mesothelial cell (OSMC) transformation. Ovarian cancer often occurs in women between 50-60 years of age. The investigators have noted that a dramatic acceleration in oocyte loss normally occurs in all women during the decade prior to menopause. Therefore, the age group most susceptible to ovarian cancer has undergone extensive oocyte loss. OCRP award recipients hypothesize that the oocyte is important for maintaining cell-to-cell communication within the ovary and that unidentified genetic modifiers function in tandem with oocyte loss to produce an abnormal microenvironment in the ovary. This altered environment may then be conducive to tumor development in the epithelial surface of the ovary. To study this possibility, a strain of mice (bclw mutant) was generated that displays accelerated oocyte death. The mice lack the bclw gene, a gene involved in the prevention of oocyte programmed cell death (apoptosis). Preneoplastic transformation of OSMC follows the premature death of oocytes in these mice. These mice represent an invaluable and unique experimental tool that can be used to characterize early events in ovarian tumorigenesis. Investigations conducted in the first year of this project confirmed the occurrence of OSMC transformation in bclw mutant female mice by 9 months of age. No evidence of progression to invasive carcinoma was found in mice greater than age 16 months. Investigators also confirmed that simultaneous inactivation of the bax gene (a pro-apoptotic gene) restores the number of oocytes in bclw mutant females to normal levels. Further genetic manipulations of this mouse strain are being investigated to characterize genetic modifiers of OSMC transformation and the conditions needed to drive OSMC transformation into invasive carcinoma.

Molecular Epidemiology of Ovarian Cancer.

David Bowtell, Peter MacCallum Cancer Institute, Melbourne, Australia: Since completion of the initial mapping of the human genome, there has been an explosion of efforts within the United States and around the world to use powerful new molecular biology techniques

"Despite increasing awareness and recent advances, ovarian cancer continues to present significant challenges to clinicians, scientists, and patients, alike. The Department of Defense's ongoing commitment to help conquer this disease through its funding of the Ovarian Cancer Research Program provides an incredible service to all women. Specifically, this program has recruited a bevy of new and talented investigators to focus their energies on unraveling ovarian cancer's challenges. It has established infrastructure at a variety of institutions that will sustain ongoing research in this field. And, it has seeded innovative projects that may open new avenues of prevention, detection, and novel therapies for this disease."

—Beth Karlan, M.D., Director, Gynecologic Oncology Research, Cedars-Sinai Medical Center, FY02 Integration Panel Chair

"It is a great privilege to play a role in such a vital research program for women's health. I am honored to work with the ovarian cancer survivors and advocates whose courage and commitment created this program; the scientists and clinicians whose vision and expertise have identified research that will most effectively move us closer to a cure; the researchers funded by this program who are rising to the challenge of eliminating this disease; and the staff at CDMRP whose energy, enthusiasm, and diligence sustain the DOD OCRP on a daily basis."

—Patricia C. Modrow, Ph.D., OCRP Program Manager

to understand the genetics of cancer. Many of these investigations link patient medical and family histories, as well as social and physical environments (epidemiology) to the newly acquired genetic data. The OCRP has recognized this worldwide effort by supporting a Program Project Award at the MacCallum Cancer Institute in Melbourne, Australia where research is being conducted to better understand the risk factors associated with ovarian cancer. A collaborative group, the Australian Ovarian Cancer Study, has been formed that includes epidemiologists and molecular biologists from Peter MacCallum Cancer Institute, the Queensland Institute of Medical Research, the University of Melbourne, Westmead Hospital and gynecological-oncologists throughout Australia. This large multicenter study will include over 1,000 women diagnosed with ovarian cancer and compare them to a similar number of women of the same age without ovarian cancer. Extensive clinical and epidemiological information will be obtained, such as oral contraceptive use, alcohol intake, and number of children, as well as pathological information. A major focus of this Program Project is to create a new classification of ovarian cancer based in part on molecular subtypes. Molecular subtype analysis involves identifying individuals with similar genetic profiles that should theoretically behave in similar ways. Another project within this study, lead by Dr. Georgia Chenevis-Trench, will collect information on the frequency of specific variant genes in women with ovarian cancer compared with women who do not have ovarian cancer. In addition, Drs. Penny Webb and Adele Green are trying to identify environmental risk factors associated with different types of ovarian cancer. Studies that do not distinguish between the different types of ovarian cancer are likely to miss factors that may only be associated with one specific type of ovarian cancer. For example, recent studies suggest that taking hormone replacement therapy may increase a woman's chances of developing ovarian cancer. However, these studies did not clearly address whether hormone replacement therapy affects all types of ovarian cancer similarly. It is anticipated that research supported by this study will inform women as to the potential risks and benefits of any therapy or behavior that may increase their risk of ovarian cancer.

Improving Quality of Life in Ovarian Cancer Patients: A Brief Intervention for Patients and Their Partners.

Sandra G. Zakowski, Ph.D., Finch University of Health Sciences/The Chicago Medical School:

Development of emotional support systems is critical for improving the quality of life for women diagnosed with ovarian cancer. Both patients and spouses/partners face a myriad of stresses related to diagnosis, treatment decisions, treatment side effects, and disruption of their normal daily lives. This stress makes the patient more prone to increased anxiety, depression, sexual problems, fear of recurrence, and uncertainty about the future. Spouses/partners overwhelmed by their own fears may be unable to provide adequate support to their partner. Therefore, psychological interventions may be needed for both patients and their spouses/partners. Dr. Zakowski, of the University of Chicago, is examining the effects of a psychological intervention that encourages emotional expression. Previous research has shown that emotional expression is regarded as a healthy process that helps people deal with stressful experiences. The expressive

writing intervention used in this study allows disclosure of very personal topics. Subjects in the intervention group will be asked to write about their deepest thoughts and feelings regarding their cancer experience for 20 minutes each day for 3 consecutive days. A control group will be asked to write about trivial nonemotional topics. Outcome variables including psychological distress, quality of life, and physical symptoms will be assessed at baseline and over a period of 9 months after the intervention (1 week, 3, 6, and 9 months). A pilot study conducted by the investigator had a 100% completion rate among patients enrolled in the study. This supports the idea that the minimal burden that this intervention poses for participants may help to maximize compliance rates as compared to more complex interventions.

Summary

Since 1997, the DOD OCRP has been responsible for managing $61.7M in congressional appropriations, which has resulted in 45 awards for FY97–01. 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.

FY02 Integration Panel Members

Chair, 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 Elect, 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.

Chair Emeritus, 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.

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.

Jeffrey Boyd, Ph.D: Associate Attending Biologist, Memorial Sloan-Kettering Cancer Center.

Mary Daly, M.D., Ph.D.: Associate Director of Cancer Control Science, Fox Chase 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.

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.

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

Stephen Rubin, M.D. Director, Division of Gynecologic Oncology, The University of Pennsylvania Medical Center.

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