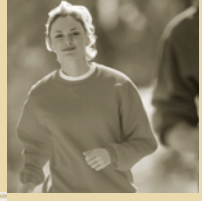
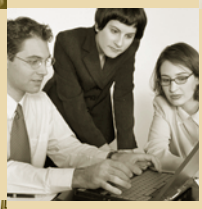






VI. Ovarian Cancer Research Program

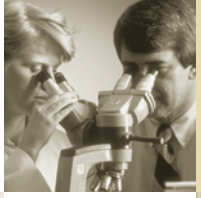
Vision: To eliminate ovarian cancer.

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: $51.5M in FY97–01, $10.2M in FY02, and $10M in FY03

Funding Summary: 45 awards from the FY97–01 appropriations; 18 awards from the FY02 appropriation; ~17 awards anticipated from the FY03 appropriation

...shaping the future of health care to prevent, control, and cure diseases.



"The importance of this program is best illustrated by the research insights provided by the fruition of the previously funded proposals. They have opened important pathways for the detection and treatment of the deadliest of the gynecologic cancers."

Patricia Goldman,
Ovarian Cancer National Alliance;
FY03 Integration Panel Member

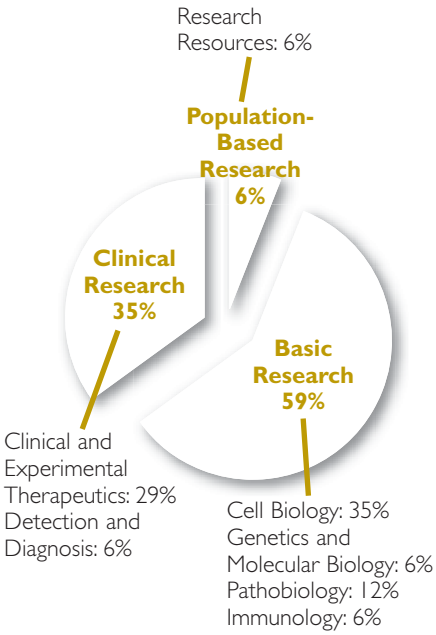


Figure VI-1. FY02 OCRP Portfolio by Research Area

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 2003, approximately 25,400 women will be diagnosed with ovarian cancer in the United States alone, and an estimated 14,300 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 percent. However, local ovarian cancer has a 95 percent 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. As a leader in extramural ovarian cancer research, the OCRP has managed $71.7M from FY97 to FY03 to fund peer reviewed ovarian cancer research. A total of 63 awards have been made through FY02 across three award categories: (1) research, (2) research resources, and (3) training/recruitment. The key initiatives of the OCRP are building research resources and supporting innovative research that will foster new directions for, address neglected issues in, and bring new independent investigators into the ovarian cancer field. Appendix B, Table B–4, summarizes congressional appropriations and the investment strategy executed by the OCRP for FY02–03.

The Fiscal Year 2002 Program

Congress appropriated $10.2M in FY02 to continue the peer reviewed DOD OCRP, marking the sixth fiscal year for this program. Two new award mechanisms were supported: Institutional Training Grants (see related box story on page VI-5) and Idea Development Awards. The Institutional Training Grants were offered to promote the training of the next generation of scientists in ovarian cancer research, while the Idea Development Awards aimed to encourage innovative approaches to

[1] *American Cancer Society - Cancer Facts and Figures 2003.*

ovarian cancer research. Of the 201 proposals received, 18 were funded, as detailed in Table VI-1. The portfolio of research supported by the FY02 OCRP is illustrated in Figure VI-1.

Table VI-1. Funding Summary for the FY02 OCRP

Category and Award Mechanism	Number of Proposals Received	Number of Awards	Investment
Research			
Idea Development	196	17	$8.3M
Training/Recruitment			
Institutional Training Grant	5	1	$0.6M
Total	**201**	**18**	**$8.9M**

The Vision for the Fiscal Year 2003 Program

Congress appropriated $10M to continue the OCRP in FY03. The program offered two award mechanisms to encourage innovative scientific ideas and approaches applicable to the etiology and early detection of ovarian cancer: Idea Development Awards and New Investigator Awards. A total of 135 proposals was received, as shown in Table VI-2, and approximately 17 awards are expected.

Table VI-2. Award Mechanisms Offered and Proposals Received for the FY03 OCRP

Category and Award Mechanism	Number of Proposals Received
Research	
Idea Development	90
New Investigator	45
Total	**135**

Scientific Outcomes and Advances

The OCRP is funding outstanding research to unravel ovarian cancer's challenges. 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.

"I was honored to serve as the Chair of the Ovarian Cancer Research Program's (OCRP) Integration Panel this past year and to have the opportunity to work with such a wonderful DOD staff. The OCRP has clearly become one of the most important sources of peer reviewed funding for cutting-edge ovarian cancer research that will ultimately lead to advances beneficial to thousands of women and their families."

David M. Gershenson, M.D.,
Professor and Chairman, Department of Gynecologic Oncology; Director, Blanton-Davis Ovarian Cancer Research Program, The University of Texas M.D. Anderson Cancer Center;
FY03 OCRP Integration Panel Chair

The Effects of a Vitamin C Derivative on Ovarian Cancer
Santo V. Nicosia, M.D., and Domenico Coppola, M.D.,
The University of South Florida

Compelling evidence indicates that certain cancers may be prevented with treatment of vitamin C and its derivatives. One such compound, ascorbyl stearate, has been shown to stop cell division and growth in brain tumor cells. Ascorbyl stearate is a promising treatment avenue as it is nontoxic and is able to easily cross biological barriers within the cell. Drs. Santo Nicosia and Domenico Coppola, who are currently funded by an FY01 OCRP Program Project award, are investigating the effects of this compound on cell division and cell death in ovarian cancer cells. Treatment of ovarian cancer cells with various concentrations of ascorbyl stearate resulted in a significant reduction in cell growth. Upon treatment, the ovarian cancer cells were "stuck" and could no longer divide. Additionally, these investigators found that ascorbyl stearate could induce cell death, as the cells could not complete the normal cell cycle. These results appear promising, as ascorbyl stearate may be a viable and nontoxic approach in combating ovarian cancer.

For additional reading about this work, please refer to the following publications:

- Nicosia SV, Bai W, Cheng JQ, et al. 2003. Oncogenic pathways implicated in ovarian epithelial cancer. *Hematol. Oncol. Clin. North. Am.* 17:927–943.
- Naidu KAA, Naidu KA, Haiyan Z, et al. Ascorbyl stearate inhibits cell proliferation and survival in human ovarian carcinoma cells by targeting PI3/AKTT2 pathway (In preparation).

Silencing Telomerase Activity in Ovarian Cancer
Patricia A. Kruk, Ph.D., and Santo V. Nicosia, M.D.,
The University of South Florida

The link between telomerases and ovarian cancer development and progression has been minimally explored. Although the primary role of telomerase is the maintenance of structural integrity at the end of chromosomes, recent studies have shown an association between telomerase activity and enhanced cell survival in various tumor types, enhancing immortalization and carcinogenesis of the cells. In the ovary, telomerase activity is silent in normal tissue as well as precancerous cells; however, the activity is "switched on" in ovarian tumor cells. OCRP-supported investigators, Drs. Patricia Kruk and Santo Nicosia, are currently

examining the cellular and molecular mechanisms by which telomerase confers resistance to standard chemotherapies. These researchers found that a particular signal transduction pathway, the PI3K/JNK pathway, may play a critical role in the regulation of telomerase in ovarian cancer. By continuing to look at these mechanisms and figuring out a way to "silence" telomerase activity, it is hoped that cancerous cells will be more susceptible to chemotherapy, thus allowing apoptosis to occur.

For additional reading about this work, please refer to the following publications:

- Alfonso-De Matte MY, Cheng JQ, and Kruk PA. 2001. Ultraviolet irradiation and dimethyl sulfoxide-induced telomerase activity in ovarian epthelial cell lines. *Exp. Cell Res.* 267:13–27.
- Alfonso-De Matte MY, Yang H, et al. 2002. Telomerase is regulated by c-Jun NH2-terminal kinase in ovarian surface epithelial cells. *Cancer Res.* 62:4575–4578.
- Alfonso-De Matte MY and Kruk PA. 2003. Phosphotidylinositol-triphosphate kinase- and c-Jun N-terminal kinase dependent induction of telomerase by calcium requires Pyk2. *Cancer Res. (*In press).
- Nicosia SV, Bai W, Cheng JQ, et al. 2003. Oncogenic pathways implicated in ovarian epithelial cancer. *Hematol. Oncol. Clin. North. Am.* 17:927–943.

Training Our Nation's Finest Researchers

Dr. Michael Seiden, Chairman of the Research Committee of the Gynecologic Oncology Program at Dana Farber Cancer Institute/Harvard Cancer Center, was the recipient of the FY02 OCRP Institutional Training Grant. This mechanism was designed to encourage the initiation of new postgraduate training programs in ovarian cancer. Dr. Seiden will be bringing together 15 outstanding faculty members from all of the major institutions and hospitals in this National Cancer Institute-designated Comprehensive Cancer Center (including Massachusetts General Hospital, Dana Farber Cancer Institute, Brigham and Women's Hospital, Beth Israel Hospital, New England Deaconess Hospital, Harvard School of Public Health, and Harvard Medical School) to mentor the next generation of ovarian cancer researchers. The faculty is building a mentoring system across multiple disciplines for exceptional postdoctoral fellows. Dr. Seiden believes that the breadth and depth of the faculty and multi-institutional resources will maximize the training experience and increase the likelihood that the talented postdoctoral trainees will become the future research leaders in the field of ovarian cancer.

The Use of the Sindbis Vector to Combat Ovarian Cancer

Daniel Meruelo, Ph.D., New York University School of Medicine

Although cisplatinum chemotherapy can achieve a response rate of 80 percent in treating ovarian cancer, a majority of patients stricken with this disease will experience recurrence. The use of gene therapy to treat cancer has gained much attention over the past 10 years. A particular type of gene therapy utilizes vectors or specific DNA sequences that can be used to transport genetic material to the host cell. These vectors can be constructed to target diseased cells in the body. OCRP researcher Dr. Daniel Meruelo is determining whether a vector based upon the Sindbis virus can be used to kill ovarian cancer cells. Dr. Meruelo observed that administration of Sinbis in conjunction with interleukin 12 (a protein capable of producing an immune response) in ovarian cancer cells resulted in cell death. In a mouse model of ovarian cancer, treatment of Sindbis–interleukin 12 extended the life of mice by 2 weeks compared to

Creating a Multicenter Resource to Study the Molecular Epidemiology of Ovarian Cancer

Professor David Bowtell of the Peter MacCallum Cancer Centre in Melbourne, Australia, in collaboration with Professor Adèle Green and colleagues at the Queensland Institute of Medical Research, Brisbane, Australia, is one of 16 recipients of the Program Project Award. These awards were first offered by the OCRP in FY97 in an effort to build research resources in the field of ovarian cancer research. Professor Bowtell was funded in FY00 to establish a multicenter population-based resource to study the molecular epidemiology of ovarian cancer. In an educational forum offered to CDMRP staff and contractors in June 2003, Professor Bowtell presented an overview of the project. He noted that the award is based upon a nationwide collaborative population-based case-control study, the Australian Ovarian Cancer Program. It relies on a unique nationwide collaboration among scientists, research nurses, data managers, and clinicians to identify patients and collect biospecimens, and epidemiological and clinical information. Cases are being identified through an existing network covering more than 85 percent of the Australian population. Upon completion, this study will be one of the largest linked biospecimen, epidemiological, and clinical information databases for ovarian cancer in the world. Professor Bowtell anticipates that this project will provide important information for ovarian cancer prevention strategies, lead to a better understanding of the pathogenesis of ovarian cancer, and create a rich biospecimen repository for future national and international studies. Additional information about the Australian Ovarian Cancer Study can be accessed on-line at http://www.aocstudy.org.

untreated mice. Although clinical trials in humans still need to be conducted, preliminary results indicate that the Sindbis–interleukin 12 combination may be a valuable treatment avenue for ovarian cancer.

Further information about this research appears in the following publications:

- Meruelo D, Levin B, and Pampeno C. 2002. Generation of packaging cell lines for the continuous production of Sindbis vectors. In *Vector Targeting for Therapeutic Gene Delivery*, DT Curiel and JT Douglas eds. New York, New York: Wiley & Sons, Inc., pp 353–375.
- Tseng J, Levin B, Hirano H, et al. 2002. Sindbis vectors mediate potent anti-tumor activity in vivo. *JNCI* 94:1790–1802.
- Ishizu A, Tsuji T, Abe A, et al. 2003. Transduction of dominant negative ATF-1 suppresses the pX gene expression in joint fibroblastic cells derived from HTLV-I transgenic rats. *Exp. Mol. Pathol.* 74:309–313.
- Tseng J-D, Levin B, Hurtado A, et al. 2003. Systemic tumor targeting and killing by sindbis viral vectors. *Nature Biotech.* Advance on-line publication, 1–8.

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 the following:

- General abdominal discomfort and/or pain (gas, indigestion, pressure, swelling, bloating, and 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.

"It is a great privilege to play a role in such a vital research program for women's health…"

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

Summary

Since 1997, the DOD OCRP has been responsible for managing $71.7M in congressional appropriations, which has resulted in 63 awards for FY97–02. The OCRP is building research resources, supporting innovative research, and training the nation's top scientists. Together, 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. Research highlights, award data, and abstracts of funded OCRP proposals can be viewed on the CDMRP website (http://cdmrp.army.mil).

Fiscal Year 2003 Integration Panel Members

David Gershenson, M.D. (Chair)
University of Texas M.D. Anderson Cancer Center

Beth Karlan, M.D. (Chair Emeritus)
Cedars-Sinai Medical Center

Ronald Alvarez, M.D. (Chair Elect)
University of Alabama at Birmingham

Mary Scroggins, M.A. (Executive Committee Member-at-Large)
Ovarian Cancer National Alliance

Debra Bell, M.D.
Massachusetts General Hospital

Jeffrey Boyd, Ph.D.
Memorial Sloan-Kettering Cancer Center

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

Patricia Goldman
Ovarian Cancer National Alliance

Thomas Hamilton, Ph.D.
Fox Chase Cancer Center

Hedvig Hricak, M.D., Ph.D.
Memorial Sloan-Kettering Cancer Center

Elise Kohn, Ph.D.
National Cancer Institute

Maurie Markman, M.D.
The Cleveland Clinic Foundation

Elwood Robinson, Ph.D.
North Carolina Central University

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