VI. 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.

Congressional Appropriations for Peer Reviewed Research:

- $61.7M in FY97–02
- $10M in FY03
- $10M in FY04

Funding Summary:

- 63 awards from the FY97–02 appropriations
- 17 awards from the FY03 appropriation
- ~12 awards anticipated from the FY04 appropriation

building critical
research
resources

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 2004, approximately 25,580 women will be diagnosed with ovarian cancer in the United States, and an estimated 16,090 will die from the disease. Ovarian cancer often is without overt or specific symptoms until late in its development; therefore, most women are diagnosed with advanced stage disease. As a result, the 5-year survival rate for all stages of ovarian cancer is 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. As a leader in extramural ovarian cancer research, the OCRP has managed $81.7M from FY97 to FY04 in an effort to eliminate ovarian cancer. A total of 80 awards have been made through FY03 across the categories of research, training/recruitment, and research resources. The key initiatives of the OCRP are building critical research resources (refer to the related box story on page VI-4 for additional reading about the program's investment in research resources), supporting innovative research, and bringing talented investigators into the ovarian cancer field. Appendix B, Table B-4, summarizes congressional appropriations and the investment strategy executed by the OCRP for FY03–04.

The Fiscal Year 2003 Program

Congress appropriated $10M in FY03 to continue the peer reviewed DOD OCRP, marking the seventh FY for this program. Two award mechanisms were supported: Idea Development Awards and New Investigator Awards. While both mechanisms encouraged innovative scientific ideas and approaches applicable to the etiology and early detection of ovarian cancer, New Investigator Awards did not require preliminary data and were directed at early-career investigators. Idea Development Awards required preliminary data and were designed for investigators at all levels of experience. Of the 135 proposals received, 17 were funded (see Table VI-1). As illustrated in Figure VI-1, the FY03 OCRP has developed a diverse research portfolio that encompasses basic, clinical, and population-based research.

Table VI-1. Funding Summary for the FY03 OCRP

Category & Award	Proposals	Awards	Investment
Research			
Idea Development	90	10	$5.3M
New Investigator	45	7	$3.3M
Total	**135**	**17**	**$8.6M**

[1] American Cancer Society - *Cancer Facts and Figures,* 2004.

"...the DOD programs have impressed me with the degree of quality of both the applications and the reviewers that are assembled to enable the program."
James P. Basilion, Ph.D., FY04 OCRP IP Member

The Vision for the Fiscal Year 2004 Program

Congress appropriated $10M to continue the OCRP in FY04. The program retained the Idea Development Awards and New Investigator Awards that were offered in the previous FY. However, emphasis was placed on tumor biology/etiology, preclinical development of targeted therapeutics, and molecular imaging/vital imaging. A total of 166 proposals were received, as illustrated in Table VI-2, and approximately 12 awards are expected.

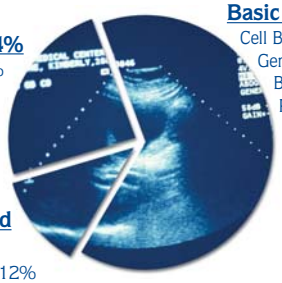

Figure VI-1. FY03 OCRP Portfolio by Research Area

Scientific Outcomes and Advances

The DOD OCRP award outcomes hold promise for eliminating this life-threatening disease. In addition to the accomplishments highlighted in the box story on page VI-5, the following projects represent some of the extraordinary advances that OCRP-funded investigators have made in the campaign against ovarian cancer.

Slow the Growth of Ovarian Cancer: The B7-H1 Blockade

Weiping Zou, Ph.D., Tulane University Health Science Center, New Orleans, Louisiana

Dr. Weiping Zou, an investigator at the Tulane University Health Science Center and recipient of an FY02 OCRP Idea Development Award, is studying the function of dendritic cells (DCs) in ovarian cancer. DCs are antigen-presenting cells in the immune system. The function of DCs is impaired in cancer patients, but the mechanism of this impairment remains elusive.

B7-H1, also called PD-L1, is a newly identified B7 family member. B7-H1 is now known to be present in human cancers including ovarian cancer. However, it was not known that this protein is present and upregulated on the surface of tumor-associated DCs until Dr. Zou's laboratory discovered that B7-H1 expression is increased in DCs under tumor environment factors. These tumor environment factors are interleukin-10 (IL-10) and vascular endothelial growth factor (VEGF). Dr. Zou and his team demonstrated that tumor environmental factors impaired myeloid DC-mediated T-cell activation by upregulating B7-H1 expression on myeloid DCs. Additionally, Dr. Zou and colleagues demonstrated that expression of myeloid DC-B7-H1 could be blocked with a specific monoclonal antibody that could activate T-cell function and decrease the production of T-cell IL-10. Furthermore, studies extended on immune-deficient mice bearing human tumors also showed that a blockade of myeloid DC-B7-H1 protein could activate a T-cell-mediated immune response.

Dr. Zou's research provides evidence that ovarian cancer growth can be slowed down significantly in the presence of a B7-H1 blockade. This finding could ultimately help investigators develop new therapeutics for treating ovarian cancer.

For additional information about this research, please refer to the following publication:

- Curiel TJ, Wei S, Dong H, et al. 2003. Blockade of B7-H1 improves myeloid dendritic cell-mediated antitumor immunity. *Nature Medicine 9(5):562–567.*

Table VI-2. Award Mechanisms Offered and Proposals Received for the FY04 OCRP

Category & Award	Proposals
Research	
Idea Development	85
New Investigator	81
Total	**166**

Development of a Novel Vaccine Using Fusion Cell Technology

Jianling Gong, M.D., Boston University, Boston, Massachusetts

Current research has found that fusion cell technology may have the potential to produce a vaccine against a broad spectrum of cancers. Fusion cell technology fuses DCs – powerful immune stimulators – and cancer cells. The fused cells are injected back into the patient to stimulate an immune response against the patient's cancer.

An Update: The Program Project Awards — Building Research Resources in the Field of Ovarian Cancer

In the 2002 Annual Report, we highlighted the essence of an OCRP Program Project. This year, we would like to report progress in this area. During the first several years of the OCRP, the program was faced with the challenge of how to best provide for the research community. From the outset, one of the main goals of the program was to establish sustained shared resources that could be used to study the disease. This goal was accomplished by funding 16 Program Projects – 15 in the United States and 1 in Australia. In funding these Program Projects, registries were developed including cell, tissue, serum, and specimen repositories (which include associated clinical and laboratory findings/data) as well as the creation of animal models that mimic ovarian cancer. The establishment of these research resources allows for future research on ovarian cancer to take place. Collectively, these OCRP Program Project investigators have published almost 100 manuscripts in a variety of peer reviewed journals, as well as presented their findings in scientific meetings throughout the world. More importantly, by supporting these Program Projects, M.D. Anderson Cancer Center, Fred Hutchinson Cancer Research Center, the Fox Chase Cancer Center, and more recently the Brigham and Women's Hospital in Boston have also been awarded National Cancer Institute Specialized Program of Research Excellence (SPORE) grants to support translational research approaches to eradicate this life-threatening disease.

This technology eliminates the need to isolate specific tumor antigens (the proteins that can trigger an immune response) as the original tumor is utilized in the fusion. In addition, scientists have found it very difficult to deliver tumor antigens into DCs. Dr. Jianling Gong, an FY99 OCRP Idea Development Award recipient, has developed a strategy to circumvent this problem. Dr. Gong has fused DCs and human ovarian tumor cells to create a hybrid cell that can initiate an antitumor response in humans. DCs were isolated from the blood of patients diagnosed with ovarian cancer and then fused with the cancerous cells from the same patients. In vitro experiments showed that these fusion cells were able to "kick-start" an immune response, and when co-cultured with ovarian cancer cells, the fusion cells were able to lyse or kill the ovarian cancer cells. Dr. Gong has received U.S. Food and Drug Administration approval to conduct a Phase 1 clinical trial of these "fusion cell" vaccines in women diagnosed with stage III/IV ovarian cancer.

Additional information about this research can be found in the following publications:

- Gong J, Nikrui N, Chen D, et al. 2000. Fusions of human ovarian carcinoma cell with autologous and allogenic dendritic cells induce antitumor immunity. *J Immunol* 165(3):1705–1711.
- Kiodo S, Ohana M, Liu C, et al. 2004. Dendritic cells fused with human cancer cells: Morphology, antigen expression, and T-cell stimulation. *Clinical Immunology* (in press).

Bottom Line

Since 1997, the DOD OCRP has been responsible for managing $81.7M in congressional appropriations, which has resulted in 80 awards for FY97–03. The OCRP's investment in research resources, innovative research, and training has aided in the national health effort to improve the well-being of all women. Research highlights, award data, and abstracts of funded OCRP proposals can be viewed on the Congressionally Directed Medical Research Programs website (http://cdmrp.army.mil).

Signs and Symptoms

Ovarian cancer is often not associated with any obvious signs or symptoms until late in its development. Some indicators 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.

"OCRP initiatives have helped recruit the brightest scientists from a variety of disciplines to focus their research on ovarian cancer."

Ronald Alvarez, M.D., FY04 OCRP IP Chair

New Ways to Identify, Treat, and Prevent Ovarian Cancer — Biomarkers, Peptides & Progestins

Because most women are diagnosed with ovarian cancer at late stages of the disease, a way to detect this disease in the early stages would save thousands of lives every year. One of the projects within Dr. Samuel Mok's Program Project Award to Brigham and Women's Hospital identified a potential biomarker, termed osteopontin, which could be used clinically to identify those women who display early signs of the disease. By testing osteopontin levels from plasma samples in both women with and without ovarian cancer, Dr. Mok and his colleagues have demonstrated that women with the disease had higher levels of this protein. Current findings suggest that osteopontin in conjunction with another protein biomarker CA125 may be even more useful in the detection of early-stage ovarian cancer, as opposed to using these two biomarkers alone.

Because most women are diagnosed with ovarian cancer at late stages of disease, a way to detect this disease in the early stages would save thousands of lives every year. The overall research focus of Dr. Sundaram Ramakrishnan's Program Project Award was to determine the role of angiogenesis or the formation of new blood vessels, in the etiology and prevention of ovarian cancer. Dr. Ramakrishnan and his team at the University of Minnesota were able to successfully re-design antiangiogenic proteins and a peptide named anginex (Dr. Kevin Mayo) that displayed the ability to slow down the growth of these blood vessels. In a human ovarian carcinoma mouse model, anginex was shown to inhibit tumor growth by 70%. Surprisingly, when anginex was combined with a chemotherapeutic agent and administered to ovarian cancer tumor-bearing mice, the tumors were barely observable. Although using anti-angiogenic drugs to treat cancer is in its early stages, the work accomplished by Dr. Ramakrishnan and his colleagues may prove to be a viable option in treating ovarian cancer in the near future.

One of the main projects under Dr. Andrew Berchuck's Program Project Award at Duke University explores the potential use of progestins, a component of oral contraceptives, as a potential ovarian cancer preventive agent. The basis for this work stems from studies in which Dr. Berchuck, Dr. Gus Rodriquez, and colleagues demonstrated that oral contraceptives have a potent apoptotic effect on ovarian epithelium and that progestin mediated this effect. Additional experiments showed that ovaries from both pre- and post-menopausal women express progesterone receptors on the ovarian epithelium and therefore may be involved in the ovary's response to progestins. Dr. Berchuck and his team are determining whether progestins will prevent ovarian cancer in chickens, the only animals with a high incidence of spontaneous ovarian cancer, with anticipation of translating this knowledge into effective preventive strategies for human ovarian cancer.

Fiscal Year 2004 Integration Panel Members

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

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

Stephen Rubin, M.D. (Chair Elect), The University of Pennsylvania Medical Center

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

James P. Basilion, Ph.D., Massachusetts General Hospital

Debra Bell, M.D., Massachusetts General Hospital

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

Kathleen R. Cho, M.D., University of Michigan Medical School

Patricia Goldman, Ovarian Cancer National Alliance

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

Elise Kohn, Ph.D., National Cancer Institute

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

Maurie Markman, M.D., University of Texas M.D. Anderson Cancer Center

Elwood Robinson, Ph.D., North Carolina Central University

"Research and investigators funded through the Ovarian Cancer Research Program are changing the landscape in terms of ovarian cancer knowledge..."

Mary Scroggins, M.A., FY04 OCRP IP Member