



**CDMRP**   
Department of Defense

Defense Health Program

# Ovarian Cancer Research Program



*U.S. Army Medical Research and Materiel Command*



# Congressionally Directed Medical Research Programs

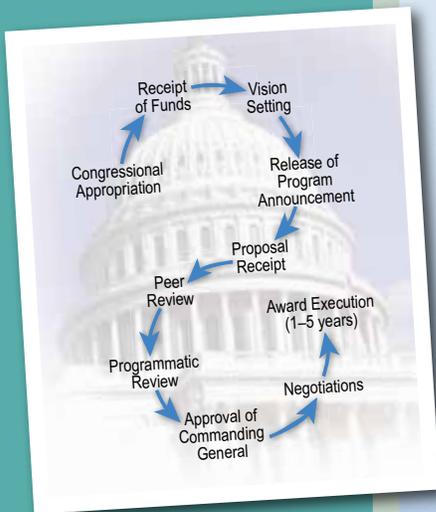
## History of the CDMRP

The office of the Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military. The success in managing the initial congressional appropriations in breast cancer research combined with additional advocacy movements and the need for focused biomedical research catapulted the CDMRP into a global funding organization for cancer research, military medical research, and other disease-specific research. The CDMRP has grown to encompass multiple targeted programs and has received \$6.25 billion in appropriations from its inception through fiscal year 2011 (FY11). Funds for the CDMRP are added to the Department of Defense (DOD) budget in which support for individual programs, such as the Ovarian Cancer Research Program (OCRP), is allocated via specific guidance from Congress.

## Proposal Review Process

The CDMRP uses a two-tier review process for proposal evaluation with both steps involving dynamic interaction between scientists and disease survivors. The first tier of evaluation is a scientific peer review of proposals measured against established criteria for determining scientific merit. The second tier is a programmatic review, conducted by the Integration Panel, which compares proposals to each other and makes funding recommendations based on scientific merit, portfolio balance, and relevance to program goals.

**This FY11 Program Book is an overview of 15 years of the DOD OCRP—the OCRP dedicates it to all of the women, families, and friends affected by ovarian cancer.**



**Congressional Appropriations for OCRP FY97–FY11**



# Ovarian Cancer Research Program

## History of the DOD OCRP

### Did you know?

- The DOD OCRP is the second-leading federal funding agency for ovarian cancer research in the United States.

In FY97, the Congressional Appropriations Conference Committee Report No. 104-863 provided \$7.5 million (M) to be administered by the DOD for ovarian cancer research. Since then, ovarian cancer survivors, scientists, and clinicians have advocated for increased public

awareness, resulting in \$20M in FY11 and a total appropriation of \$180.45M to the OCRP. To target critical research and to be responsive to the needs of the ovarian cancer community, the OCRP evaluates and refines its goals annually.

The DOD OCRP is always looking at new ways to drive scientific progress to impact ovarian cancer. As a leader in funding extramural ovarian cancer research, the DOD OCRP is investing in high-impact, innovative research that continues to fulfill unmet needs and push the field of ovarian cancer forward. A total of 236 awards were made through FY10.

## Key Initiatives of the DOD OCRP

- Leverage critical research resources
- Challenge current thinking and approaches
- Support conceptually innovative research
- Accelerate movement of promising ideas into clinical applications
- Support partnerships between clinicians and laboratory scientists
- Facilitate multidisciplinary and nontraditional collaborations
- Foster the next generation of ovarian cancer researchers

### Did you know?

- In 2011, approximately 21,990 new cases of ovarian cancer will be diagnosed in the United States, and an estimated 15,460 women will die from this disease.

## VISION

Eliminate ovarian cancer.

## MISSION

To support research to detect, diagnose, prevent, and control ovarian cancer.

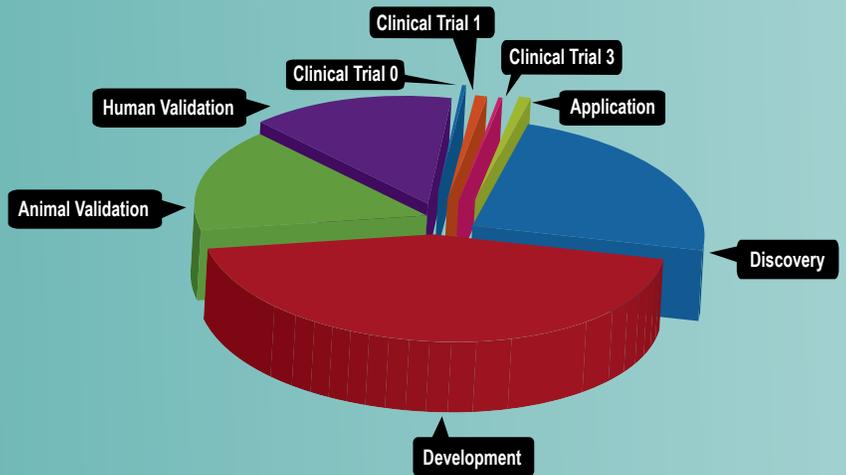


Dr. Zhen Zhang,  
FY03 Idea  
Development  
Award

“Research partially supported by my DOD Idea Development grant has led to the discovery of biomarkers that have become part of OVA1, the first-ever proteomic IVDMA (in vitro diagnostic multivariate index assay) cleared by FDA for clinical use. OVA1 is indicated for the presurgical evaluation of women with an ovarian mass and suspicion of an ovarian neoplasm.”

# THE DOD OCRP TREK: ADDRESSING UNMET NEEDS BY SETTING PRIORITIES AND SUPPORTING CUTTING-EDGE RESEARCH

OCRP Research Phases, FY97–FY09



Since its inception, the DOD OCRP has been filling unique niches by encouraging and supporting research in areas that are unmet within the ovarian cancer community. The DOD OCRP has accomplished this by thinking differently, creating novel award mechanisms, setting focus areas, and supporting diverse and nontraditional partnerships.

## 1997 *Beginning of the DOD OCRP*

- » First DOD OCRP appropriation
- » Ovarian cancer advocates launch grassroots campaign to increase research funding

## 1997, 1998, 2000, 2001 *Building Critical Resources*

- » Focused on novel prevention strategies, etiology, early detection, preclinical therapeutics, quality of life via Program Projects
- » Established shared resources, including ovarian cancer tissues and linked clinical data, International Ovarian Cancer Association Consortium, and the Australian Ovarian Cancer Study (AOCS)

## 1999, 2002–2011 *Supporting Innovative Research*

- » Supported creative research ideas that were high risk but had the potential for high return

## 1999–2000, 2005–2006 *Bringing Talented Investigators into Ovarian Cancer Research*

- » Developed junior faculty and career transition independent researchers
- » Supported HBCU/MI\* investigators in developing research resources and careers

\*Historically Black Colleges and Universities/Minority Institutions

## Did you know?

- Ovarian cancer is not a “silent killer.” In June 2007, a consensus statement agreeing that ovarian cancer has specific symptoms was released.

### 2007–2011

#### **Translational Research**

- » Supported innovative translational research to accelerate promising ideas toward clinical applications

#### **Collaborations**

- » Supported partnerships between clinicians and laboratory scientists to transform ideas into clinical applications
- » Created the Translational Leverage Award to leverage existing human-based ovarian cancer resources in translational research

### 2009

#### **Creating a Collaborative and Interactive Research Training Environment**

- » Created the Ovarian Cancer Academy, a unique, interactive virtual group that provides focused mentoring, national networking, and a peer group for junior faculty.
- » Offered the first nested Teal Predoctoral Scholar option to foster the next generation of ovarian cancer investigators through mentored research training

### 2008–2010

#### **Initiating Ground-Breaking Research in Detection of Early-Stage Disease**

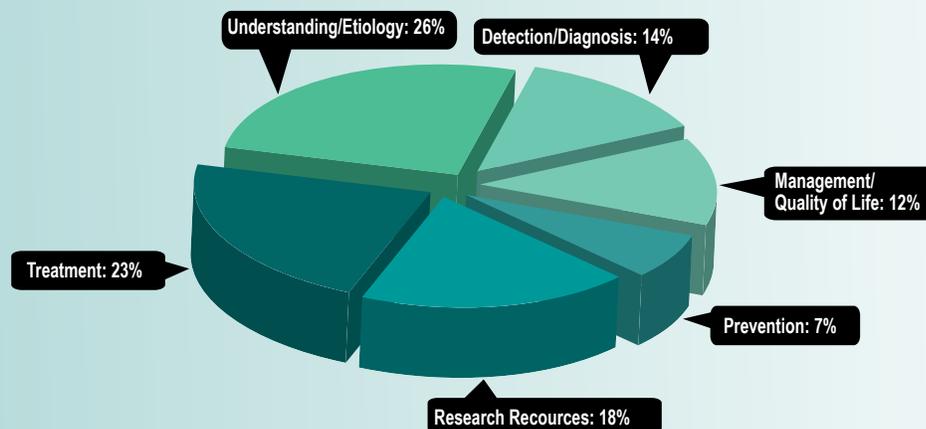
- » Supported the Consortium, a major multi-institutional research effort that specifically focuses on identifying and characterizing early changes of disease associated with ovarian cancer.

### 2010–2011

#### **Leveraging Resources**

- » Created the Translational Leverage Award to leverage existing human-based ovarian cancer resources in high-impact translational research

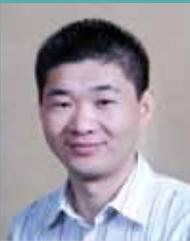
OCRP Portfolio Study Areas, FY97–FY10



**Excerpt of Statement to the House Defense Appropriations Subcommittee Thursday, May 20, 2010 at 10:00 am DOD OCRP: A Testimony to 15 Years of Supporting Scientific Successes Daniel L. Clarke-Pearson, M.D. President - Society of Gynecologic Oncologists Professor and Chair, Obstetrics and Gynecology University of North Carolina Medical School Chapel Hill, North Carolina On Behalf of The Society of Gynecologic Oncologists**

## Did you know?

- Ovarian cancer causes more deaths than any other cancer of the female reproductive system
- Only 15% of all ovarian cancer cases are detected at the localized stage
- Overall, the 1-, 5-, and 10-year relative survival rates are 75%, 46%, and 35%, respectively.



**Dr. Rugang Zhang, FY09 Ovarian Cancer Academy Early Career Investigator**

“DOD OCRP provides a unique platform for cutting-edge research to greatly impact ovarian cancer intervention and prevention, represents a critical venue for translational ovarian cancer research, and plays a pivotal role in launching my research program in ovarian cancer.”

I am honored and pleased that this subcommittee is focusing its attention on the Department of Defense (DOD) Congressionally Directed Medical Research Program in Ovarian Cancer (OCRP). Since its inception now 13 years ago, this DOD program has delivered benefits to ovarian cancer research that far exceed the annual level of Federal funding.

Ovarian cancer causes more deaths than all the other cancers of the female reproductive tract combined, and is the fourth highest cause of cancer deaths among American women. Unfortunately, most ovarian cancer is diagnosed at late or advanced stage, when the 5-year survival rate is only 31%. ..... yet funding for gynecologic cancer research, especially for the deadliest cancer that we treat, ovarian cancer, has been relatively flat. Were it not for the DOD OCRP, many researchers might have abandoned their hopes of a career in basic and translation research in ovarian cancer and our patients and the women of America would be waiting even longer for reliable screening tests and more effective therapeutic approaches.

The SGO is a national medical organization of physicians who are trained in the comprehensive management of women with malignancies of the reproductive tract. The members of the SGO, along with our patients who are battling ovarian cancer every day, depend on the DOD OCRP research funding. It is through this type of research funded by the DOD OCRP that a screening and early detection method for ovarian cancer can be identified which will allow us to save many of the 15,000 lives that are lost to this disease each year.

### **Department of Defense Ovarian Cancer Research Program: Building an Army of Ovarian Cancer Researchers**

Since its inception in FY 1997, the DOD OCRP has funded 214 grants totaling more than \$150 million in funding. The common goal of these research grants has been to promote innovative, integrated, and multidisciplinary research that will lead to prevention, early detection, and ultimately control of ovarian cancer. Much has been accomplished in the last decade to move us forward in achieving this goal.

### **Department of Defense Ovarian Cancer Research Program: Exemplary Execution with Real World Results**

The OCRP is able to reset the areas of research focus on an annual basis, by using the mechanism of an Integration Panel (IP). The IP actively manages and evaluates the OCRP current grant portfolio and funds gaps in ongoing research. Most importantly the IP funds high risk/high reward studies to take advantage of the newest scientific breakthroughs that can then be attributed to better treatments for ovarian cancer.

Over the decade that the OCRP has been in existence, the 209 grantees have used their DOD funding to establish an ovarian cancer research enterprise that will hopefully bring us by the end of the second decade of this program to our ultimate goal of prevention, early detection and finally elimination of ovarian cancer.

The full statement can be accessed at [www.sgo.org/workarea/downloadasset.aspx?id=3650](http://www.sgo.org/workarea/downloadasset.aspx?id=3650)

## OCRP:

# Continuing to Move the Field Forward in FY11

The DOD OCRP's overall goal is to eliminate ovarian cancer by supporting innovative, high-impact research. To achieve this goal, the OCRP promoted unique partnerships between laboratory scientists and clinicians and nontraditional partners through the Translational Research Partnership Award and Idea Development Award; fostered the next generation of ovarian cancer investigators through the unique, virtual Ovarian Cancer Academy; and supported a major multi-institutional research effort that specifically focuses on the identification and characterization of early changes of disease associated with ovarian cancer with the Consortium Award. The FY11 OCRP continues to focus on innovative, high-risk/high-reward research that may lead to critical discoveries or major advancements through the Pilot Award. The Translational Pilot Award seeks innovative translational research addressing a critical problem or question in ovarian cancer that will accelerate promising ideas toward clinical applications.

Three new award mechanisms are also on the horizon for the FY11 OCRP. With the novel Translational Leverage Award, the OCRP seeks to leverage existing human-based ovarian cancer resources. Often, resources are not leveraged for maximum use beyond the original source, and as a result, investigators expend time and money to duplicate those resources. This award mechanism is focused on leveraging existing human-based resources in translational research to address high-impact research ideas or unmet needs in ovarian cancer. The Teal Innovator Award provides a visionary individual with the funding and freedom to pursue his/her most novel, high-risk ideas that could significantly impact the field of ovarian cancer research or patient care. The Teal Expansion Award supports the expansion of a previously OCRP-funded awardee's original research idea or the generation of a new idea based on the original research project.

### Did you know?

- Since inception of the DOD OCRP, ovarian cancer survivors have participated in establishing the OCRP's priorities, research funding opportunities, and funding recommendations

#### Dr. John H. Farley Integration Panel Member

"OCRP has led the research into the development of biomarkers that could be fundamental to the development of a blood test for diagnosis of early-stage disease and isolation of cancer stem cells from epithelial ovarian cancer to someday allow for the development of targeted therapies."

# Strategic Partnerships

The success of the DOD OCRP can be attributed to the synergistic efforts of many talented and dedicated individuals. The strategic partnerships between the military, ovarian cancer consumer advocates, clinicians, and scientists have helped shape the DOD OCRP and accelerate science. Through this partnership, ovarian cancer consumer advocates work together with scientists and clinicians to identify research that will lead to the understanding, early detection, diagnosis, prevention, and management of ovarian cancer.

The two-tier review process utilized by the OCRP brings together ovarian cancer survivors' firsthand perspectives with the expertise and knowledge of scientists and clinicians on the peer and programmatic review panels. More than 530 scientists, clinicians, and ovarian cancer consumer advocates have participated in scientific peer review for the OCRP. The peer review panels, organized by scientific discipline, provide expert advice on the scientific and technical merit of research proposals as well as the impact of the proposed research. The OCRP Integration Panel, composed of scientists, clinicians, and consumer advocates who are leaders in their fields, provides vision for the OCRP with each year's appropriation. The Integration Panel refines program priorities and investment strategies that reflect the needs of the ovarian cancer community and makes funding recommendations that best meet the program's goals.

Ovarian cancer consumer advocate participation is a critical factor in the success of the DOD OCRP. The unique experiences of the consumer advocates complement the expertise of the scientists and clinicians who serve on both the peer and programmatic review panels. The voice of the ovarian cancer survivor brings a sense of urgency and the human dimension of the disease into the DOD OCRP's policy, investment strategy, and research focus. This perspective helps scientists and clinicians understand how the research will impact the community and, moreover, encourages funding recommendations that reflect the concerns of consumer advocates and their families as well as the clinicians who treat them.

## Did you know?

- More than 130 ovarian cancer survivors have participated as equal voting members at both scientific peer review and programmatic review.

# Early Detection and Diagnosis

Early detection and diagnosis of ovarian cancer remain a challenge. Currently, there is no early detection or screening test for ovarian cancer. However, there are tests for women who are at high risk for the disease, including the CA-125 blood test, transvaginal ultrasound, and pelvic exam. In 2007, the Ovarian Cancer Symptoms Consensus Statement noted that ovarian cancer is not a “silent killer,” and the following symptoms are much more likely to occur in women with ovarian cancer than women in the general population: bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, and urinary symptoms (urgency or frequency).

Investigators believe that it is possible to detect early ovarian cancer for all women. Ovarian Cancer Research Program (OCRP) researchers are working toward the development of novel, minimally invasive tests for early detection and diagnosis.

## MicroRNAs: Potential Biomarkers for Early-Stage Ovarian Cancer

**Muneesh Tewari, M.D., Ph.D., Fred Hutchinson Cancer Research Center, Seattle, Washington**

Ovarian cancer frequently remains asymptomatic until an advanced stage. Therefore, development of a blood test that can accurately detect ovarian cancer at an early, curable stage is desperately needed. Dr. Muneesh Tewari, with funding from an FY08 Career Development Award, is investigating the sensitivity and specificity of microRNAs as biomarkers for the early detection of ovarian cancer. Preliminary studies have demonstrated that levels of a specific microRNA are significantly different in a test set of ovarian cancer plasma samples compared to healthy controls, suggesting that it is a novel ovarian cancer biomarker. Dr. Tewari's research team is currently validating these findings by investigating the expression of the microRNA biomarker in plasma from women with early stages of ovarian cancer and comparing these levels to expression in late-stage ovarian cancer.

## A Novel Method of Early Detection

**Patricia Kruk, Ph.D., University of South Florida, Tampa, Florida**

While the early detection of ovarian cancer can save women's lives, there is still no reliable method of detecting the disease. Dr. Patricia Kruk, an FY06 Idea Development Award recipient, is working to change this. In previous studies, Dr. Kruk found that Bcl-2 (an anti-apoptotic protein) can be detected in the urine of ovarian cancer patients. She is conducting studies using a simple, commercially available enzyme-linked immunosorbent assay to validate Bcl-2 as a urinary biomarker for ovarian cancer. To date, Dr. Kruk demonstrated that the commercially available assay adequately detects Bcl-2. When compared to healthy controls and women with benign gynecologic disease, she observed that urinary levels of Bcl-2 were elevated in ovarian cancer patients regardless of patient age, tumor grade, stage of ovarian cancer, histologic subtype, and creatinine levels. Additionally, urinary levels of Bcl-2 were elevated in ovarian cancer patients but not in individuals with other types of reproductive and nonreproductive cancers. If validated, measuring Bcl-2 would provide a novel, simple, and cost-saving method of detecting ovarian cancer that could benefit all women, including those who are at high risk for the disease or live in medically underserved areas. Dr. Kruk surmises that measuring urinary Bcl-2 could be used to monitor disease and help predict therapeutic and prognostic outcomes as well.

### Did you know?

- Women diagnosed with early-stage ovarian cancer have a 5-year survival rate of ~93.8%.



**Dr. Patricia Kruk,  
University of South  
Florida, FY99  
New Investigator  
and FY06 Idea  
Development  
Awards**

“Given the mission of the Ovarian Cancer Research Program to fund high-risk projects, my lab has been able to carry out innovative research, which we hope will lead to the development of a simple and reliable urinary test for ovarian cancer—the deadliest gynecologic malignancy. This could benefit women worldwide, improve survival from ovarian cancer, and reduce lifelong medical costs.”

# The Ovarian Cancer Consortium Award

The DOD Ovarian Cancer Consortium Award is an exciting research opportunity that has the potential to significantly impact ovarian cancer incidence and mortality. While much has been gained in the knowledge about ovarian cancer over the past decade, overall survival has not appreciably improved in the past several decades. The OCRP believes that this award will help elucidate the precursors of ovarian cancer and provide a greater understanding of the early events associated with the disease.

## From the Researcher's Perspective

**Robert Kurman, M.D., Johns Hopkins University, Baltimore, Maryland**



The incidence and overall mortality of ovarian cancer has not changed appreciably in the past 50 years, and there is currently no effective screening strategy. This is due, in large part, to an inadequate understanding of the early events in ovarian carcinogenesis. The notion that ovarian carcinoma originates in the ovarian surface epithelium (OSE) or in ovarian cortical inclusion cysts (CICs) has been the teaching for decades, but there is a lack of consensus among investigators that this is in fact true. Moreover, the prevalence of these changes is very low. Recently, morphologic, immunohistochemical (IHC), and molecular genetic evidence has been advanced, implicating a lesion in the fallopian tube (particularly in the fimbria) designated "serous tubal intraepithelial carcinoma (STIC)" as a precursor of ovarian high-grade serous carcinoma (HGSC). STICs are found in association with ovarian HGSC in 50%–60% of cases and in the fallopian tubes of high-risk women undergoing prophylactic bilateral salpingo oophorectomy in approximately 10%–15% of cases.

Our consortium includes Johns Hopkins University, Memorial Sloan-Kettering Cancer Center, Yale University, and the University of Toronto Health Network. By pooling the resources from these four institutions, we will accumulate a sufficient number of cases that will offer a unique opportunity to investigate these competing views regarding early ovarian carcinogenesis. Our hypothesis is that STIC is the precursor of many, if not most, HGSCs; however, we will also investigate the other proposed candidates (OSE and CICs). If our hypothesis is validated, it would support our overall objective, which is to develop a prevention strategy to reduce the burden of this disease. With support from an OCRP Program Project grant and New Investigator Awards, we have previously developed a dualistic model of ovarian carcinogenesis (type I and type II cancers) that links specific histologic types of ovarian cancer with specific precursors based on pathologic, molecular genetic, and clinical features. Thus, STICs are related to only type II tumors, specifically HGSC. This has particular significance since HGSC represents 75% of all ovarian cancers and accounts for 90% of the deaths.

Our consortium studies will focus exclusively on the early events associated with HGSC and not on any of the other

histologic subtypes. There will be four preclinical projects and one epidemiology project that will utilize morphologic, molecular biologic, and IHC techniques as well as in vitro and mouse models to validate our hypothesis that the precursor of many, if not most, HGSCs begins in the fallopian tube, which would then provide the scientific underpinning for future clinical prevention studies. Current clinical approaches to the management of ovarian cancer have focused on radical surgery, cytotoxic chemotherapy, and early detection but never on prevention. A successful prevention approach has the potential of dramatically reducing mortality and would have the added benefit of preserving fertility in young women and preventing loss of hormonal function in older women. For example, if our hypothesis is even partially correct, salpingectomy or even fimbriectomy (removal of the part of the fallopian tube close to the ovary where most precursor lesions develop) could be offered to women who are at high risk of ovarian cancer as well as women in the general population who are seeking a more permanent form of contraception. Tubal ligation is not likely to be as effective since this procedure only removes a small portion in the middle of the tubes and leaves the fimbria intact. Since epidemiology studies have consistently shown that a reduction in ovulation (either from oral contraceptive pill [OCP] usage or multiple pregnancies/lactation) significantly reduces the frequency of ovarian cancer, we will explore the relationship of ovulation to ovarian carcinogenesis to determine if OCPs or other related compounds (possibly anti-inflammatory agents) can provide medical-type prevention. Last, many older women who have hysterectomies for benign uterine disease often undergo bilateral removal of the ovaries and fallopian tubes to reduce their risk of ovarian cancer. It has been shown, however, that compared to ovarian conservation, removal of the ovaries, particularly in younger women, increases mortality from all causes and increases the risk of coronary artery disease. Elimination of elective oophorectomy in these women, which is performed only to reduce ovarian cancer risk, would have enormous impact since approximately 300,000 women undergo removal of their ovaries annually in the United States.

Accordingly, if our studies confirm that many HGSCs begin in the fallopian tube and involve the ovary secondarily, prevention, by targeting early lesions in the fallopian tube, could have a similarly profound effect on reducing ovarian cancer mortality as cytology screening had for cervical cancer.

# Understanding Ovarian Cancer

New discoveries are helping scientists, clinicians, and women understand more about the development and progression of ovarian cancer. OCRP researchers are taking unique approaches to gain a deeper understanding of ovarian cancer that will ultimately benefit women affected by the disease.

## Structural and Functional Analysis of CA125: Potential for Early Diagnosis and Understanding the Immune Evasion Strategies of Epithelial Ovarian Tumors

**Manish Patankar, Ph.D., University of Wisconsin, Madison, Wisconsin**

Dr. Manish Patankar, of the University of Wisconsin, Madison, received an FY03 Idea Development Award from the DOD OCRP. The award supported Dr. Patankar's investigation into the biological role of the ovarian tumor mucin MUC16, a large molecular weight molecule that contains repeating peptide epitopes more commonly known as CA125. Funding from the award helped Dr. Patankar and his coinvestigators demonstrate that ovarian cancer cells use MUC16 to metastasize in the peritoneal cavity. The research team conducted studies to define the kinetics of MUC16 binding to mesothelin, a glycoprotein expressed on mesothelial cells. The binding of MUC16 to mesothelin allows cancer cells to attach to the mesothelial cells. The researchers further demonstrated that removal of the N-linked oligosaccharide chains of MUC16 inhibits the binding ability of the mucin to mesothelin.

Dr. Patankar and his colleagues demonstrated that in addition to aiding in the metastasis of ovarian cancer cells, MUC16 is a potent inhibitor of the cytotoxicity of human natural killer (NK) cells. NK cells are a major arm of the innate immune system, and they mediate an anti-cancer response. Analysis of NK cells and monocytes isolated from the peripheral blood and peritoneal fluid of ovarian cancer patients showed that these immune cells were positive for MUC16. The team conducted extensive experiments proving that the immune cells were not expressing endogenous MUC16 but were instead binding to the mucin that was being released by the ovarian cancer cells. The researchers have now demonstrated that MUC16 binds to the I-type lectin Siglec-9, which is expressed by NK cells and monocytes. Siglec-9 is an inhibitory receptor, and the researchers believe that the binding of MUC16 to Siglec-9 results in negative signaling in the immune cells whereby they are unable to react against the ovarian cancer cells. In addition to suppressing immune cell function via Siglec-9, MUC16—because of its large size and high negative charge—also shields the ovarian cancer cells from NK cells. Thus, the ovarian cancer cells are utilizing MUC16 as a major mechanism to evade immune attack.

The binding of MUC16 to the immune cells suggests that, in addition to determining the serum levels of CA125, immune cell-bound MUC16 may also serve as an alternate method for diagnosis and monitoring of ovarian cancer. Indeed, Dr. Patankar's data indicate that the immune cell-bound MUC16 provides positive results even when the serum CA125 levels are low to undetectable. The group is conducting analysis of serial samples isolated from ovarian cancer patients to determine if the immune cell-bound MUC16 can serve as a better marker for disease recurrence than the serum CA125 assay. These observations have also led Dr. Patankar and his team to investigate whether there may be other biomarkers, in addition to MUC16, in the transcriptome and proteome of immune cells of ovarian cancer patients. These new studies are the basis for Dr. Patankar's FY10 Pilot Award through the OCRP—Mining the Immune Cell Proteome to Identify Ovarian Cancer-Specific Biomarkers.

### Did you know?

- Epithelial ovarian cancer is the most common type, accounting for approximately 90% of ovarian cancers.





## Characterizing and Targeting Ovarian Cancer

**Susan K. Murphy, Ph.D., Duke University, Durham, North Carolina**

Susan K. Murphy is an assistant professor in the departments of Obstetrics and Gynecology and Pathology at Duke University. A common theme in many of Dr. Murphy's publications is the molecular basis of ovarian cancer. Her research interests include identification of methylation biomarkers of disease, ovarian cancer stem cells, chemotherapeutic response in ovarian cancer, tumor dormancy and the influence of the in utero environment on DNA methylation, and risk of disease.

Dr. Murphy received an FY04 OCRP Idea Development Award entitled, "Epigenetic Characterization of Ovarian Cancer," which sought to understand the contribution of epigenetic regulation, an alternative form of gene regulation, to ovarian cancer. Her team identified and validated a large number of genes that were targeted by DNA methylation as a mechanism to repress their transcription. Her findings are important not only because they add significantly to our knowledge about the gene set that becomes epigenetically deregulated in ovarian malignancies but because they also have the potential to directly affect patient care. In the greater research world, her work has generated a great deal of interest as is evident in the publications and five successful funding applications resulting from this work.

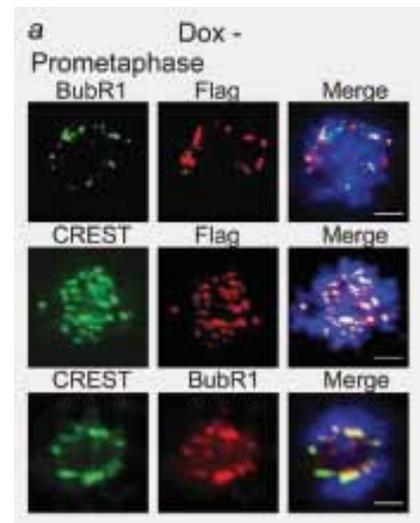
In FY10, Dr. Murphy received a Translational Pilot Award for her project, "Preemptive Approach to Improving Survival in Epithelial Ovarian Cancer." Her objective is to determine whether drugs that more effectively kill slow-growing cells are able to reduce or eliminate tumor growth in a mouse model of recurrent ovarian cancer. Hopefully, this study will be a springboard for the initiation of clinical trials that may lead to incorporation of her approach in treating women with advanced-stage ovarian cancer. While patients are typically treated with drugs that only target fast-growing cancer cells, Dr. Murphy's research, should it yield promising results, may increase the number of survivors because patients will receive additional treatment (likely while in remission) to eradicate the remaining slow-growing cells.



## Discovering a New, Potential Target for Ovarian Cancer

**Kathleen M. Mulder, Ph.D., Penn State Hershey College of Medicine, Hershey, Pennsylvania**

Dr. Kathleen M. Mulder, an FY02 Idea Award recipient, discovered that the protein km23 functions as a motor receptor, which plays an important role in transporting transforming growth factor beta (TGF $\beta$ ) signaling components to their respective sites of action. Mutations in km23 can alter TGF $\beta$  signaling events. When km23 is highly overexpressed in cells, the protein can kill human ovarian cancer cells in a mouse model in vivo. Dr. Mulder is using km23 as a target for the development of new ovarian cancer therapeutics that can mimic km23's role in killing ovarian cancer cells. In addition, Dr. Mulder has a U.S. patent for an ovarian cancer screening assay for women with km23-dependent ovarian cancer, which requires additional investigation prior to translation to the clinic.



Dox SKOV-3 cells. km23-1 is present with BubR1 at the kinetochore in prometaphase, whereas in metaphase, km23-1 is localized at the kinetochore and/or along MT spindles while BubR1's localization is aberrant. Kinetochore immunostaining studies in SKOV-3 clone #14 Dox cells were described in "Material and Methods." DAPI (blue) staining shows chromosomes. Merge depicts colocalization of the relevant components.

## Identifying Factors in Aggressive Ovarian Cancer

**Tian-Li Wang, Ph.D., Johns Hopkins University, Baltimore, Maryland**

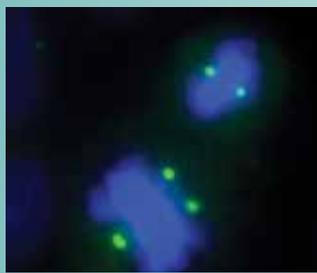
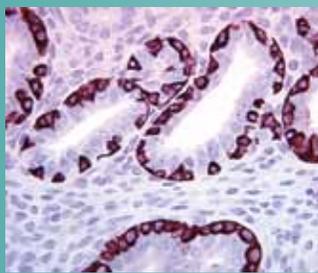
Dr. Tian-Li Wang, an FY04 New Investigator awardee, studied the progression of ovarian cancer by analyzing the genomes and gene expression of a series of ovarian cancer tumors. She found that the genes *Rsf-1* and *Notch3* were the most likely to have extra copies in the genome of these cancer cells, and these copies correlated to a similarly large amount of the protein. Comparison of survival rates found that patients with higher levels of *Rsf-1* had shorter survival rates than women with normal expression levels. A separate set of experiments looked at deleted areas of the ovarian cancer genome from these samples and found that mitogen-activated protein kinase kinase 4 (*MKK4*, or *MAP2K4*) was deleted in 40% of tested samples; in fact, a reduction in the expression of this protein was seen in 75% of tested serious carcinomas compared to normal ovarian tissue. These results identify potentially important proteins to target for ovarian cancer therapy in *Rsf-1* and *Notch3*, and a potential diagnostic and therapeutic target in *MAP2K4*. Based on results from this grant, Dr. Wang received funding from the National Institutes of Health, the American Cancer Society, and the Ovarian Cancer Research Fund, helping to expand her work in the ovarian cancer field.



## Mouse Model for Hereditary Ovarian Cancer

**Sandra Orsulic, Ph.D., Women's Cancer Research Institute at Cedars-Sinai Medical Center, Los Angeles, California**

With funding from an FY03 New Investigator Award, Dr. Sandra Orsulic developed a novel mouse model that has led to a better understanding of events that contribute to the initiation and progression of hereditary ovarian cancer. Hereditary ovarian cancer patients carry a genetic mutation of the tumor suppressor gene *Brca1*. Patients with *Brca1* mutations typically develop ovarian cancer 10 years earlier than patients who develop sporadic ovarian cancer. Dr. Orsulic's research team generated mouse ovarian epithelial cancer cell lines lacking the *Brca1* gene to identify biochemical pathways involved in hereditary ovarian cancer initiation and progression. They determined that the accumulation of additional genetic mutations resulting in the loss of *p53* along with an increase in *Myc* initiated ovarian cancer. These studies have furthered the understanding of events involved in early breast cancer progression. In addition, implantation of these cancer cell lines into mice resulted in the development of serous ovarian cancer, the most common type of hereditary ovarian cancer. The development of these novel ovarian cancer cell lines has provided the ovarian cancer research field with an innovative experimental system for evaluating therapies specific for this aggressive form of ovarian cancer.



### Did you know?

- Relative survival varies by age. Women younger than 65 are twice as likely to survive 5 years (57%) after diagnosis than women 65 years of age and older (29%).

# Risk and Prevention

## Did you know?

- One in 71 women will develop ovarian cancer in her lifetime.

Ovarian cancer prevention is an important issue, especially for those women who are at high risk for developing the disease. Approximately 10%–15% of ovarian cancers are hereditary, and mutations in the BRCA1/2 genes result in 5%–10% of ovarian cancers. There are also environmental factors that may contribute to ovarian cancer risk. OCRP investigators are employing innovative approaches to understanding risk factors of ovarian cancer and potential methods for prevention.



## Mumps Parotitis and Ovarian Cancer: Modern Significance of an Historic Association

**Daniel W. Cramer, M.D., Sc.D., Brigham and Women's Hospital, Boston, Massachusetts**

A study from 1966 found that women with ovarian cancer were less likely to report having childhood mumps than women with benign ovarian cysts suggesting mumps may be protective against ovarian cancer. Additional epidemiologic studies confirmed that a history of mumps may be associated with a lower risk for ovarian cancer, but none of these studies offered a clear explanation as to why. Dr. Daniel W. Cramer of Brigham and Women's Hospital, an FY06 Concept Award recipient, decided to look for a biological reason for this long-forgotten association. Previously, Dr. Cramer had looked at levels of antibodies against a glycoprotein related to CA125 called mucin 1 (MUC1), which is expressed in many tissues as well as the cancers that arise from these tissues. He found that higher levels of anti-MUC1 antibodies occurred in women who had had a tubal ligation or breast mastitis—events that may decrease ovarian cancer risk. Based on these findings, he hypothesized that the expression of a tumor-like form of MUC1 during an acute inflammatory event, like mumps parotitis, may induce anti-MUC1 antibodies, which could later recognize the same form of MUC1 from an early ovarian tumor and lead to an immune reaction that could eliminate an early ovarian tumor—a process called immunosurveillance.

In his study, Dr. Cramer summarized data from eight case-control studies related to mumps and ovarian cancer and showed the summary results were consistent with a protective effect of mumps parotitis against ovarian cancer. Surveying health agencies and obtaining specimens that had been collected from individuals with a mumps infection, he measured levels of anti-MUC1 antibodies, MUC1, and CA-125 in serum samples comparing the mumps cases to healthy age- and sex-matched controls. As hypothesized, he observed that anti-MUC1 antibody levels were higher in cases with mumps than the controls, particularly in younger individuals and females. CA-125 was also higher in the serum of cases. Dr. Cramer concluded that additional studies about the specific immune changes that occur during a mumps infection may further explain its potential beneficial effect on ovarian cancer and provide clues for duplicating this effect in the post-vaccination era when childhood mumps seldom occurs.

### Reference:

Cramer DW, Vitonis AF, Pinheiro SP, McKolanis JR, Fichorova RN, Brown KE, Hatchette TF, and Finn OJ. Mumps and ovarian cancer: Modern interpretation of an historic association. *Cancer Causes Control*. 2010;21:1193-201.2951028.



**Ms. Judi Gordon,  
Integration  
Panel  
Member**

"It is a great privilege to serve as a consumer advocate on the DOD OCRP Integration Panel to help bring some of the concerns of the survivor community to the discussion. As an equal voting member, I have been treated with respect by the physicians and scientists who sit on this panel as we all strive to fund proposals that further the research on ovarian cancer. My fervent wish is that our work will make a difference in the lives of women with this disease."

## The Impact of the Australian Ovarian Cancer Research Study: From the Researcher's Perspective

**David Bowtell, Ph.D., Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia**

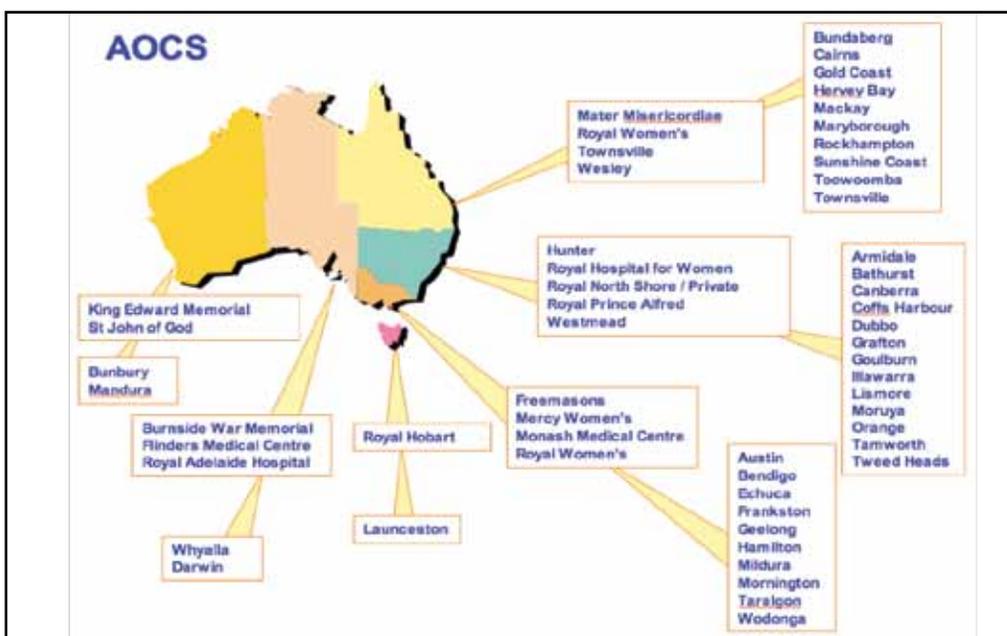
Surgery followed by a combination of carboplatin and taxol form the mainstay of treatment for women with ovarian cancer. About 70% of those with the most common histotype, high-grade serous cancers, have a durable response to chemotherapy. However, the tumors of a significant fraction of women are resistant to primary treatment with a rapid return to growth soon after the end of chemotherapy. In 2009, Dr. Bowtell's team demonstrated that amplification of the 19q12 chromosomal locus is the most important chromosomal copy number change associated with primary treatment failure. In his latest work, he has shown that CCNE1, which encodes cyclin E1, is a driver oncogene within the 19q12 locus. Knockdown of CCNE1 results in cell cycle arrest and attenuation of clonogenic survival specifically in cells with amplification of 19q12, demonstrating an oncogene addiction of these tumor cells. Cyclin E1 interacts with cell cycle kinases, including Cdx2, providing a therapeutic approach to inactivating the protein complex using small-molecule inhibitors of kinase function. Approximately 20% of high-grade serous cancers have amplification of the 19q12 locus.

The AOCS has been a major contributor to the international Ovarian Cancer Association Consortium (OCAC), which aims to find common polymorphisms that alter susceptibility to ovarian cancer. The OCAC has so far published some results from the first genome-wide association study for ovarian cancer, which has identified five susceptibility loci to date, including risk alleles at 9p22.2 and 19p13. Additional candidates are currently being followed up on by the OCAC with the long-term aim of developing risk prediction models for ovarian cancer that include information on genetic and environmental risk factors.

The Translational Research Partnership Award has allowed Dr. Bowtell's team to examine the prevalence of BRCA 1 and BRCA2 germline mutations in a population-based series of 1,000 women with invasive epithelial ovarian cancer to gain a better understanding of the likelihood of germline mutation in different patient subsets and the impact of BRCA mutations on treatment response and outcome. Findings suggest that BRCA mutations form a substantial proportion of ovarian cancer and provide important prognostic and predictive information. A substantial change in genetic testing guidelines for women with ovarian cancer is therefore warranted, and Dr. Bowtell proposes that mutation testing should be integrated into the initial management of all patients with invasive epithelial ovarian cancer.

The OCRP was key to the establishment of the AOCS, providing program funding in the 2000 round. Between 2002–2006, AOCS recruited more than 2,500 women presenting for surgery for suspected ovarian cancer, including more than 1,800 women with confirmed borderline or invasive cancer, making it one of the largest resources for ovarian cancer research in the world. An OCRP Translational Research Partnership award in 2007 allowed Dr. Gillian Mitchell and Dr. David Bowtell to investigate germline BRCA mutations in more than 1,000 women with ovarian cancer. The soon-to-be-released findings have important implications for guidelines for genetic testing and chemotherapy management in ovarian cancer.

**David Bowtell, Ph.D.  
FY00 Program Project  
and FY09 Translational  
Research Partnership  
Awards**





## Searching for Trends in Ovarian Cancer

**Delores Grant, Ph.D., North Carolina Central University, Durham, North Carolina**

Developing new ovarian cancer researchers is essential to future successes in the field. Dr. Delores Grant was awarded an FY07 HBCU/MI (Historically Black Colleges and Universities/Minority Institutions) Fellowship to develop her epidemiological knowledge to conduct analyses within the North Carolina Ovarian Cancer Study, a population-based, case-control study of Caucasian and African American patients. In collaboration with Duke University Medical Center, Dr. Grant has published a study based on this data set that indicates women who were at least 35 years old at last pregnancy have a twofold increase in risk for peritoneal primary cancer but a decreased risk for epithelial ovarian cancer. This information highlights that the two types of cancer likely have different molecular triggers, adding support to their distinction as two separate diseases. She continues to conduct molecular studies, including a study looking at the UDP-glucuronosyltransferase 2B family of enzymes (proteins) that normally help remove androgen hormone (involved in prostate cancer development) from tissues. These studies increase current knowledge of ovarian cancer development in addition to training a new ovarian cancer researcher.

## Testing the Chemopreventative Ability of COX-2 Inhibitors in the Laying Hen

**Mack N. Barnes, M.D., University of Alabama, Birmingham, Alabama**

The majority of women diagnosed with ovarian cancer already have an advanced stage of the disease, limiting treatment options and conveying a high risk of mortality. Potential preventive strategies are a useful tool in reducing the overall number of women developing ovarian cancer. Dr. Mack N. Barnes was awarded an FY03 Idea Development Award to explore whether using COX-2 inhibitors could reduce the incidence of ovarian carcinogenesis. Earlier studies suggested the possibility that non-steroidal anti-inflammatory drugs (NSAIDs) may be chemopreventive in other types of cancer. COX-2 inhibitors are a type of NSAID that target the COX-2 enzyme and avoid some of the gastrointestinal symptoms that are often a side effect of extended NSAID use. Dr. Barnes used laying hens as a model of spontaneous ovarian carcinogenesis, as they show an increased risk with age, treating them for a period of 12–22 months. Of 304 4-year-old hens, more than 60% developed reproductive tract adenocarcinomas, but a comparison between the control and treatment groups did not show a difference in the development of these tumors or in tumor volume. However, this study did give further evidence that this model may be a useful means of evaluating spontaneously developing ovarian tumors (and the means of preventing them) in a way that mouse models have not been able to fulfill.

### Did you know?

- Women who have used oral contraceptives for 5 or more years have ~50% lower risk of developing ovarian cancer than those who have not.

# Treatment and Recurrence

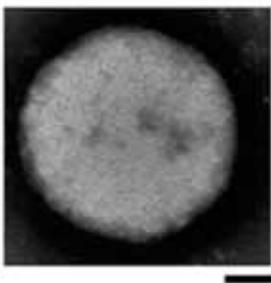
While most ovarian cancers respond to initial chemotherapy and/or radiation treatments, approximately 70% of women diagnosed with ovarian cancer will have a recurrence. OCRP investigators are conducting groundbreaking research into treatments for primary and recurrent disease.

## Did you know?

- Ovarian cancer is the fifth-leading cause of cancer death in women.

## Targeting Ovarian Cancer with Nanoparticles

**Martin L. Yarmush, M.D., Ph.D., Massachusetts General Hospital, Boston, Massachusetts**



Transmission electron microscopic image of the formed particles. Scale bar = 100 nm.

Dr. Martin L. Yarmush, recipient of an FY06 Concept Award, has developed heterogeneous nanoparticles that may provide a novel method of targeting and treating ovarian cancer metastases. A product of the fusion of elastin-like polypeptides with targeting and proapoptotic peptides, these nanoparticles caused apoptosis (cell death) in ovarian cancer cells with high specificity and efficiency. Dr. Yarmush's research is ongoing and will be extended to include imaging/diagnostic components. If successful, his work may lead to a new, targeted therapy that maximizes ovarian cancer cell death while minimizing systemic side effects.

## Targeting Cyclin E Processing

**Christine Walsh, M.D., Cedars-Sinai Medical Center, Los Angeles, California**

Previously, cyclin E (a member of the protein family that controls the cell cycle) over-expression was identified as a recurrent genetic event in high-grade papillary serous ovarian cancer, and it was observed that deregulation of cyclin E causes chromosomal instability, a feature of epithelial ovarian cancer. Based on these findings, Dr. Christine Walsh hypothesized that cyclin E deregulation may be an early event in ovarian cancer carcinogenesis. With her Career Development Award, Dr. Walsh is generating a mouse model to study initial genetic changes in epithelial ovarian cancer. She also found a novel drug combination that appears to be effective in killing ovarian cancer cells. The natural dietary phytochemical, indole-3-carbinol (I3C), is known to disrupt cyclin E processing. While the proteasome inhibitor, bortezomib, is minimally effective against ovarian cancer as a single agent, Dr. Walsh observed that I3C sensitized multiple ovarian cancer cell lines to bortezomib. This discovery may have the potential to move bortezomib from the bench to the clinic as another option for treating ovarian cancer.



## Did you know?

- Ovarian cancer is the ninth most common cancer among women.

## Gene Therapy: A Novel Therapeutic Approach

**David Curiel, M.D., Ph.D., Washington University School of Medicine, St. Louis, Missouri**

Gene therapy is a novel therapeutic approach that has the potential to control carcinoma in the ovary; however, highly efficient gene delivery vectors would be essential to make this approach clinically successful. Dr. David Curiel, an FY04 Idea Development Award recipient, suggested using a double-targeting, adenoviral-based method that would achieve such an improvement in gene therapy. Through this award, Dr. Curiel developed adenoviral vectors that are beneficial for double targeting and identified both the tumor promoters for targeting ovarian cancer as well as the adenoviral modifications that augmented gene delivery for the tumor targets. Dr. Curiel also created a novel ovarian cancer mouse model that allows for light-based imaging analysis thereby giving him the ability to monitor tumor growth inhibition and identify the optimal double-targeting adenoviral agent. This innovative, double-targeting, adenoviral-based therapy could have an impact on disease management and has strong translational potential.

## Developing a Multivalent Therapeutic Vaccine

**Michael Morse, M.D., Duke University, Durham, North Carolina**

**Ramila Philip, Ph.D., Immunotope, Inc., Doylestown, Pennsylvania**

To address issues of platinum resistance, the overall goal of Drs. Ramila Philip and Michael Morse is to develop a multivalent immunotherapeutic vaccine that could be administered with chemotherapy or other targeted therapies. Through their FY07 Translational Partnership Award, they have successfully identified nine potential vaccine candidate epitopes that are overrepresented in platinum-resistant ovarian cancer cells. These candidate antigens may lead to a novel immunotherapy that will help mitigate this major issue in ovarian cancer treatment and progressive disease. Drs. Philip and Morse have developed a method of differential immunoproteomics analysis that will help them isolate additional immunotherapeutic targets in ovarian cancer and other cancers as well.



Ramila Philip



Michael Morse

## Treatment with Naproxen Inhibits Ovarian Cancer Metastasis

**Laurie Hudson, Ph.D., University of New Mexico, Albuquerque, New Mexico**

With funding from an FY07 Concept Award, Dr. Laurie Hudson and Dr. Angela Wandinger-Ness have identified the R-enantiomer of the nonsteroidal anti-inflammatory drug (NSAID) naproxen as a potential therapy to inhibit ovarian cancer cell metastasis. This exciting finding not only supports the benefits of select NSAIDs for the treatment of ovarian cancer, but it also has significant implications for new directions in ovarian cancer therapeutic drug targeting. Drs. Hudson and Wandinger-Ness noted that R-naproxen, but not the commercially available S-enantiomer, inhibited certain small GTPases and was predicted to dock to the nucleotide binding site of the small GTPase Rac1. Small GTPases regulate many cellular functions, including movement (trafficking) of proteins in cells, cell adhesion, and migration. High levels of the epidermal growth factor receptor (EGFR) are frequently associated with poor patient prognosis, and Dr. Hudson's research team investigated the effect of naproxen in regulating EGFR trafficking in ovarian cancer cells.

Interestingly, treatment of ovarian cancer cells with R-naproxen not only resulted in EGFR retention in the interior of the cell but also inhibited cancer cell migration and invasion, whereas S-naproxen did not modulate these cell functions. These results indicate that R-naproxen may inhibit ovarian cancer cell metastasis. Dr. Hudson determined that R-naproxen was regulating the activation of Rac1 and Cdc42 small GTPases, suggesting a novel therapeutic ovarian cancer drug target.

### Did you know?

- Women diagnosed with late-stage ovarian cancer have a 5-year survival rate of 28%.

## Focusing on Treatments for Advanced-Stage Ovarian Cancer

**Xiaoliu Zhang, M.D., Ph.D., Baylor College of Medicine, Houston, Texas**

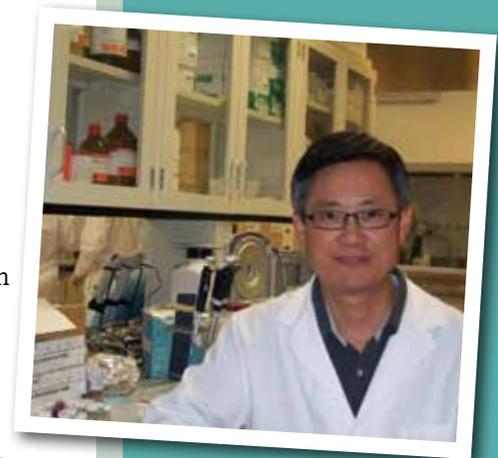
Women diagnosed with advanced ovarian cancer have a lower 5-year survival rate than women diagnosed at an early stage. Given the poorer prognosis, there is a need for improved treatments for advanced-stage ovarian cancer. FY02 Idea Development awardee Dr. Xiaoliu Zhang is developing a fusogenic oncolytic virus therapy for the treatment of advanced ovarian cancer. He has shown that incorporating a hyperfusogenic glycoprotein into an oncolytic herpes simplex virus (HSV) through a novel controlling mechanism significantly enhances the antitumor potency of the virus without significantly increasing its toxicity. When compared to a nonfusogenic virus, in vitro characterization of a doubly fusogenic oncolytic HSV (Synco-2D) showed a significant increase in tumor cell killing ability. When injected directly into the abdominal cavity of mice bearing human ovarian cancer xenografts, Synco-2D eradicated all tumor masses in 75% of the animals whereas no animals in the conventional oncolytic HSV-treated group were tumor free. These findings hold promise for a future ovarian cancer therapy, and one of the oncolytic viruses that was studied during the funding period is currently being evaluated for translation into clinical testing for treating solid tumors (including ovarian cancer).



## Genes to Predict Ovarian Cancer Response to Chemotherapy

**Dong Liang, Ph.D., Texas Southern University, Houston, Texas**

Although chemotherapy treatment with paclitaxel and carboplatin is the standard of care for patients with advanced-stage ovarian cancer, individual therapeutic responses to this treatment vary greatly. Dr. Dong Liang, with funding from an FY06 HBCU/MI Collaborative Research Award, is investigating the genetic variables that impact ovarian cancer patient response to chemotherapy as well as associated treatment side effects. This pivotal research will enable clinicians to individualize chemotherapy treatment plans to maximize tumor response while limiting carboplatin- and paclitaxel-related toxicities. Dr. Liang and his collaborators Drs. Karen Lu and Xifeng Wu at the University of Texas M.D. Anderson Cancer Center have shown that nucleotide excision repair genes, matrix metalloproteinase genes, TGF $\beta$  pathway genes, and microRNA polymorphisms are responsible for the variability in patient response to chemotherapy treatment. Validation of these important findings is ongoing and may lead to the development of a rapid screen able to predict individual ovarian cancer response to treatment.



**Ms. Karen Mason,  
Integration  
Panel  
Member**

“The importance of risk in ovarian cancer research is becoming more and more relevant in these slow economic times. Many researchers and patients alike are beginning to believe that taking great risks may be the path to bring about desperately needed changes in the ovarian cancer world. If we can imagine it, it can happen...Perhaps in the near future more federally funded organizations will follow the path of the Department of Defense’s Ovarian Cancer Research Program and begin to think ‘outside of the box.’

“One of my favorite proposals that came to fruition was the creation of The Ovarian Cancer Academy. This academy provides enticements so that new researchers will head into the area of ovarian cancer research. The academy offers funding, mentorship, and accessibility to peers who share the same interest. In today’s world too many researchers are heading into areas where money is more accessible. The academy is one way to keep the pipeline open for ovarian cancers researchers.”

# Ovarian Cancer Academy

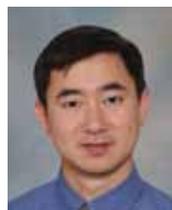
## Freshman Year

The Ovarian Cancer Academy, a virtual career development and research training platform, is in full swing during its first year. This unique academy brings together a group of like-minded, talented, and highly committed early-career investigators, their mentors, and the academy Dean, and provides them with adequate research funding and opportunities to establish these early-career investigators as the next generation of successful ovarian cancer researchers. The academy began the year with a face-to-face meeting during which the academy early-career investigators presented their proposed work, networked among themselves and their mentors to establish near-term collaborations, and brainstormed about laboratory management techniques, acquiring leadership qualities, establishing goals, extracting good feedback, and committing to being a lifelong learner, speaking intelligently and passionately to “grab” an audience—important tools that they will use throughout their careers. An important aspect of the Ovarian Cancer Academy is collaboration. During this first year of the academy, the early-career investigators have embraced collaboration and networking within and outside of the academy. In addition to the activities shown throughout these two pages, the early-career investigators have collaboratively presented in workshops, networked during international conferences, and discussed their work in teleconferences. The DOD OCRP is proud of their career and research accomplishments, and looks forward to their continued success and development as they become leaders in ovarian cancer research.



### Martina Bazzaro, University of Minnesota, Minneapolis, Minnesota

- Bazzaro M, et al.  $\alpha,\beta$ -Unsaturated carbonyl system of chalcone-based derivatives is responsible for broad inhibition of proteasomal activity and preferential killing of human papilloma virus (HPV) positive cervical cancer cells. 2011. *J Med Chem*, Jan 27;54(2):449-56.
- Partnered with a tissue bank and therefore gathered tissue samples of different grades, stages, and malignancy
- Journal review: *Journal of Medicinal Chemistry* and *Journal of Solid Tumors*
- Mentoring two clinical fellows and several laboratory members
- Organizing seminars for women's health
- Member, editorial board, *Gynecological Oncology* journal



### Jeremy Chien, Mayo Clinic College of Medicine, Rochester, Minnesota

- Awarded FY10 CDMRP Translational Pilot Award: “Ovarian Mouse Models with Targeted Fallopian Tubal Carcinogenesis”
- Li Y, et al. FusionHunter: Identifying fusion transcripts in cancer using paired-end RNA-seq. 2011. *Bioinformatics*, May 5.
- Gonzalez Bosquet J, et al. Comparison of gene expression patterns between avian and human ovarian cancers. 2011. *Gynecol Oncol*, Feb;120(2):256-64.
- Journal review: *Neoplasia*, *BMC Cancer*, *Cancer*, *Journal of Biological Chemistry*, and *Genomics*
- Mentoring one postdoctoral fellow and three summer undergraduate students



### Panagiotis Konstantinopoulos, Harvard Medical School, Cambridge, Massachusetts

- Konstantinopoulos PA, et al. Integrated analysis of multiple microarray datasets identifies a reproducible survival predictor in ovarian cancer. 2011. *PLoS One*, Mar 29;6(3): e18202.
- Konstantinopoulos PA, et al. Gene expression profile of BRCAness that correlates with responsiveness to chemotherapy and with outcome in patients with epithelial ovarian cancer. 2010. *J Clin Oncol*, Aug 1;28(22):3555-61.
- Presenter, National Cancer Institute Translational Science Meeting
- Promoted from instructor to assistant professor
- Member, editorial board, *Journal of Clinical Oncology* (official journal of ASCO)
- Mentoring a hematology/oncology fellow and an internal medicine resident

**Academy  
Dean,  
Patricia  
Donahoe,  
M.D.**



### **Charles Landen, University of Alabama at Birmingham, Birmingham, Alabama**

- Landen CN, Jr, et al. Targeting aldehyde dehydrogenase cancer stem cells in ovarian cancer. 2010. *Mol Cancer Ther*, Dec;9(12):3186-99.
- Landen CN, et al. Tumor-selective response to antibody-mediated targeting of alphavbeta3 integrin in ovarian cancer. 2008. *Neoplasia* 10(11): 1259-67.

- Acquiring new laboratory space
- Peer reviewer, CDMRP and Ontario Institute of Cancer
- Board of directors, Foundation for Women's Cancer
- Mentoring an M.D./Ph.D. student
- Leading resident research program
- Member, editorial board, *Gynecological Oncology* journal



### **Kathryn Terry, Harvard Medical School, Boston, Massachusetts**

- Permuth-Wey J, et al. LIN28B polymorphisms influence susceptibility to epithelial ovarian cancer. 2011. *Cancer Res*, Jun 1;71(11):3896-3903.
- Terry KL. MTHFR polymorphisms in relation to ovarian cancer risk. 2010. *Gynecol Oncol*, Nov;119(2):319-24.
- Poster, internal breast/gynecologic meeting

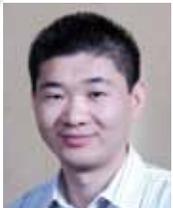
- Supervising two postdoctoral fellows
- Instructor, Epidemiologic Methods in Obstetrics and Gynecology



### **Anda Vlad, University of Pittsburgh School of Medicine and Magee-Womens Research Institute, Pittsburgh, Pennsylvania**

- Budiu RA, et al. Soluble MUC1 and serum MUC1-specific antibodies are potential prognostic biomarkers for platinum-resistant ovarian cancer. 2011. *Cancer Immunol Immunother*.
- Vlad AM, et al. A phase II trial of intraperitoneal interleukin-2 in patients with platinum-resistant or platinum-refractory ovarian cancer. 2010. *Cancer Immunol Immunother*, Feb;59(2):293-301.

- Mentoring two postdoctoral fellows, a graduate student, a medical student, and a high school student
- Her postdoctoral fellow presented on her behalf at a regional conference and won first place prize
- Co-organizer, retreat in women's cancer research center



### **Rugang Zhang, Fox Chase Cancer Center, Philadelphia, Pennsylvania**

- Li H, Cai Q, Godwin AK, and Zhang R. Enhancer of zeste homolog 2 promotes the proliferation and invasion of epithelial ovarian cancer cells. 2010. *Mol Cancer Res*, Dec;8(12):1610-8.

• Kennedy AL, et al. Activation of the PIK3CA/AKT pathway suppresses senescence induced by an activated RAS oncogene to promote tumorigenesis. 2011. *Mol Cell*, Apr 8;42(1):36-49.

- Project leader of Ovarian Cancer Research Fund grant
- Currently reviewing for 10 journals
- Appointed to serve with an experimental therapeutics Gynecology Oncology group at the National Institute of Health National Cancer Institute
- Peer reviewer, CDMRP



# Achievements at a Glance: Making an Impact

## **Dr. Zhen Zhang – OVA1™ Helps Determine Whether an Ovarian Mass Is Malignant**

Developed OVA1™, the first IVDMA (in vitro diagnostic multivariate index assay) of proteomic biomarkers cleared by the U.S. Food and Drug Administration to help physicians determine if a pelvic mass is benign or malignant before it is removed. This information will help physicians identify patients who should be referred to a gynecologic oncologist.

## **Dr. Martin McIntosh – MMP7 and Early Detection of Ovarian Cancer**

Discovered that MMP7 is elevated in serum up to 3 years prior to diagnosis of ovarian cancer.

## **Dr. Janet Sawicki – Nanoparticle Delivery of a Suicide Gene for Ovarian Cancer Treatment**

Developed a targeted treatment using nanoparticles to deliver diphtheria toxin-encoding DNA to ovarian cancer cells, leaving healthy cells unaffected.

## **Dr. Nouri Neamati – SC144, A Novel Anti-Cancer Agent**

Validated SC144 (small-molecule inducer) as a novel anticancer agent that could be used to develop combination therapies for drug-sensitive and drug-resistant ovarian cancer.

## **Drs. Santo Nicosia and Jin Cheng – API-2/Tricirbine Inhibits Akt-Activated Cancers**

Discovered API-2/tricirbine (now in Phase I clinical trials as VQD-002), a compound that potentially inhibits Akt-activated cancers, which includes more than 40% of ovarian tumors.

## **Dr. Sundaram Ramakrishnan – Anginex Inhibits Angiogenesis in Ovarian Cancer**

Developed anginex, a potent antiangiogenic and anticancer peptide that shows efficacy in combating ovarian cancer. PepTx, Inc., founded by Dr. Ramakrishnan's Program Project collaborator, Dr. Kevin Mayo, produces anginex, which is marketed by Phoenix Pharmaceuticals.

## **Dr. Richard Pietras – Squalamine Enhances the Effectiveness of Chemotherapy**

Developed and patented treatment of ovarian cancer with squalamine in combination with other anticancer agents/modalities (now in Phase II clinical trials through Genaera Pharmaceuticals).

## **Dr. Martin Cannon – Stimulating CD8+ T Cell Response Against Ovarian Tumor Antigens**

Demonstrated that enhancing the CD8+ T cell response to ovarian cancer reduces the size of tumors in 75% of cases without surgery or chemotherapy.

## **Dr. Rebecca Liu – Ovarian Cancer Cells Sensitive to Resveratrol**

Showed that ovarian cancer cells are sensitive to glucose deprivation and resveratrol treatment when compared to control cells and that resveratrol can inhibit the PI3K/Akt/Tor pathway in ovarian cancer cells.

## **Dr. George Coukos – Promising Panel of Biomarkers**

Discovered a panel of 13 promising genes that were selected for further validation as ovarian cancer biomarkers. Evidence showed that nine of these tumor vascular markers were expressed in the tumor vasculature in vivo, indicating that they are candidates for imaging or therapeutic targeting (patent is pending for the tumor vascular markers and methods of use thereof). Now in Phase I clinical trial.

## **Dr. Andrew Berchuck – Ovarian Cancer Genetic Association Study and OCAC**

Founded the International Ovarian Cancer Association Consortium. Currently validating the finding from Dr. David Bowtell's Program Project that +331A allele of PR gene is significantly associated with protection against endometrioid ovarian cancer.

## **Dr. David Bowtell – Valuable Population-Based Resources**

Built a multicenter, population-based resource involving the collection of linked epidemiologic and clinical data and biospecimens from 2,003 cases and 1,073 matched controls (1,719 questionnaires, more than 1,600 blood samples, and 1,100 frozen tissue samples) to study ovarian cancer risk factors and biomarkers.

## **Dr. Igor Jurisica – Computational Biology Technologies to Identify Biomarkers**

Created OPHID/I2D, online databases of known and predicted protein-protein interactions (PPIs), and NAViGaTOR, a software package for visualizing and analyzing PPI networks.

# Looking to the Future

## **Dr. Animesh Barua – Contrast-Enhanced Ultrasound-Targeted Imaging**

Supporting the development of an early detection test for ovarian cancer using markers in the blood and noninvasive, tumor-targeted ultrasound imaging with enhanced resolution.

## **Dr. Laurence Cooper – T Cell-Targeted Therapy**

Supporting the development of innovative technology to enhance the therapeutic potential of T cells by modifying them to express an ovarian cancer-specific chimeric antigen receptor.

## **Dr. Daniela Dinulescu – Stem Cells and Platinum Resistance**

Supporting the characterization of cancer stem cells' roles in precursor lesions, tumor progression, and platinum chemoresistance.

## **Dr. Shai Izraeli – Novel Treatment**

Supporting the suppression of STIL gene activity in sporadic ovarian cancer to make them highly sensitive to conventional and newer chemotherapy treatments that are only effective for BRCA1/2 hereditary ovarian cancer.

## **Dr. Sally Kornbluth – Regulating Ovarian Cancer Cell Death**

Supporting the study of whether interrupting biochemical pathways that link glucose metabolism and the caspase 2 enzyme will make ovarian cancer cells more responsive to chemotherapy.

## **Dr. Ramadeep Rattan – Diet Modulation and AMPK**

Supporting the investigation of whether diet modulation will activate AMPK (AMP-activated protein kinase) and change the metabolic state of cancer cells to affect ovarian cancer progression and patient outcomes.

## **Dr. Eleanor Rogan – Estrogen-DNA Adducts as Novel Biomarkers for Ovarian Cancer**

Supporting the investigation of mutations in enzymes in estrogen metabolism pathways and whether women with epithelial cancer have high levels of estrogen-DNA adducts to determine whether changes in enzymes are related to high levels of DNA-adducts and epithelial ovarian cancer.

## **Dr. Jian-Ping Wang – Magneto-resistive Nanosensors**

Supporting the development of sensitive, giant, magneto-resistive, nanoparticle-based sensors to detect serum biomarkers.

## **Dr. Ralph Weissleder – Novel Magnetic Resonance Detection and Profiling**

Supporting the optimization, application, and refinement of an innovative technological platform (diagnostic magnetic resonance) to detect ovarian cancer cells and biomarkers.

## **Dr. Lily Wu – Tumor-Infiltrating Myeloid (TIM) Cells**

Supporting the investigation of TIM cells' role in aggressive ovarian cancer and whether blocking their recruitment/function will enhance the antiangiogenic therapy's effectiveness.





For more information, visit  
<http://cdmrp.army.mil>  
or contact us at:  
[CDMRP.PublicAffairs@amedd.army.mil](mailto:CDMRP.PublicAffairs@amedd.army.mil)  
(301) 619-7071

