



Department of Defense
Congressionally Directed Medical Research Programs

Ovarian Cancer Research Program

Congressionally Directed Medical Research Programs



HISTORY OF THE CDMRP

In 1992, the Office of the Congressionally Directed Medical Research Programs (CDMRP) was born from a powerful grassroots effort led by the breast cancer advocacy community that convinced Congress to appropriate funds for breast cancer research. This enabled a unique partnership among the public, Congress, and the military. Created within the U.S. Army Medical Research and Materiel Command to manage these critical funds, the CDMRP has grown to encompass multiple targeted programs and has received over \$4.7 billion in appropriations from its inception through fiscal year 2008 (FY08). Funds for the CDMRP are added to the Department of Defense (DOD) budget, where support for individual programs such as the Ovarian Cancer Research Program (OCRP) is allocated via specific guidance from Congress.

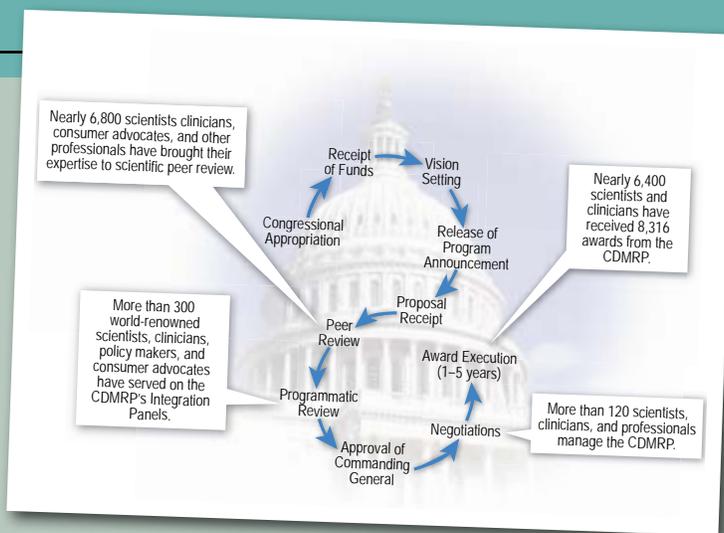
PROPOSAL REVIEW PROCESS

The CDMRP uses a two-tier review process for proposal evaluation, with both steps involving dynamic interaction between scientists and disease survivors. Scientific reviewers and other professionals are selected for their subject matter expertise while consumer reviewers provide a perspective that is complementary to the scientific expertise. The consumer group evaluates proposals based on the impact the research will have on the disease and how it will translate effectively to the patient.

Overall, consumer reviewers bring a sense of urgency to the discussions.

The first tier of evaluation is a scientific peer review of proposals weighed against established criteria for determining scientific merit. Proposals that advance to the second tier face a programmatic review that is conducted by an Integration Panel (composed of scientists, clinicians, and consumers) that

compares submissions to each other and recommends proposals for funding based on scientific merit, portfolio balance, and relevance to program goals.



Ovarian Cancer Research Program

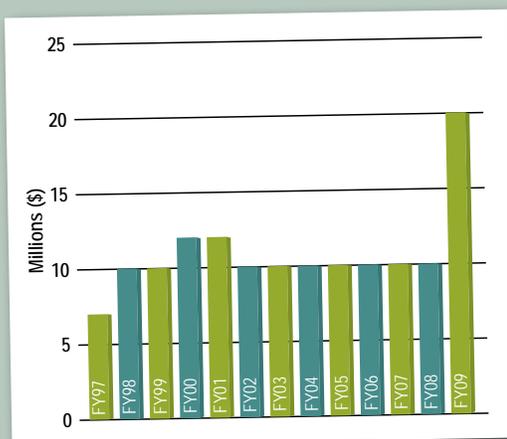
HISTORY OF THE OCRP

Efforts by ovarian cancer advocates led to a congressional appropriation of \$7.5 million (M) in FY97 to establish the DOD OCRP. As a major leader in extramural ovarian cancer research, the OCRP managed \$141.7M from FY97 to FY09 in an effort to eliminate the disease. Key initiatives of the OCRP have included supporting critical research resources, funding innovative research, and bringing talented investigators into the field of ovarian cancer research.

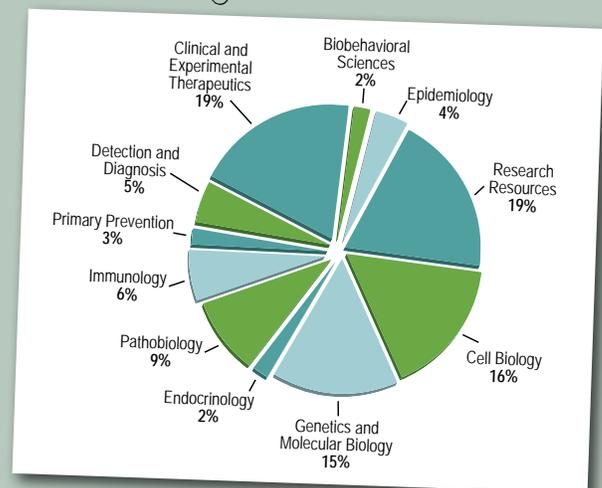
Since the inception of the program, the OCRP Integration Panel has invested 31% of its funding in the areas of cell biology, genetics, and molecular biology. As the initiating events of ovarian cancer are still unknown, a lack of knowledge in these areas hampers scientists' efforts to develop an early screening test. Because the majority of ovarian cancer patients have recurrences of their disease, improving treatment is also a very important area of research, and the OCRP has

invested 19% of its funding in this area. Funds also have been granted for research resources, such as tissue repositories, databases, biomarkers, and animal models, so ovarian cancer researchers may share their knowledge to further the study of this disease.

Congressional Appropriations for the OCRP FY97-FY09



The OCRP Portfolio Categorized by Research Area



Consumer Involvement Voicing the Research Needs of the Consumer Community



A UNIQUE FEATURE OF THE OCRCP—CONSUMER ADVOCATES

As active members of the OCRCP, consumer advocates participate in proposal review while also working to establish program priorities and funding recommendations. Since 1997, over 80 consumer advocates have served on peer and programmatic review panels for the OCRCP. Firsthand experience with ovarian cancer provides each consumer advocate with a unique perspective that complements the expertise of the scientists and clinicians on the panels. Moreover, this perspective helps scientists understand the human side of how the research will impact the community, encouraging funding recommendations that reflect the concerns of patients, the clinicians who treat them, and the survivors and their families. Equally important, consumer advocates take what they have learned back to their communities to increase awareness of the importance of cancer research. This communication helps to strengthen the relationship between the scientific community and the consumer advocate community.



"Participating in this program has been one of the most rewarding experiences of my life. As cancer victims, we often feel isolated and hopeless. Being a consumer reviewer made me feel like I was doing something to restore the peace and stability I once enjoyed in life. Seeing the honesty, integrity, and brilliance of the people involved in the program gives me great hope for the future."

Dr. Shannon Walker, Peer Review Consumer Reviewer, FY07–FY08

"As an ovarian cancer stage IIIc survivor, I have lobbied on Capitol Hill every year since 2002 for the Ovarian Cancer Research Program. Our efforts for [FY]09 have already begun, and our hope is to obtain \$25 million. I am honored to be a member of the Integration Panel and to have a voice representing all ovarian cancer survivors when it comes to determining what research the DOD funds."

Ms. Karen Mason, Integration Panel Member, FY07–FY08



"In 1993 I was diagnosed with ovarian cancer and, despite having been raised in a medical family, had never heard of a specialty called gynecologic oncology. All I knew was that Gilda Radner had ovarian cancer and that most women who had it died. After going through the treatment regimen standard for that time, I began to search for an ovarian support group that would be similar to the breast cancer groups. Although I discovered there weren't any such groups, I did become aware of other women around the country who had embarked on the same search. We eventually met at meetings convened by the Department of Defense (DOD) to create the DOD Ovarian Cancer Research Program in 1997. An outgrowth of these acquaintances and meetings was our formation of the Ovarian Cancer National Alliance. The Alliance has since become the major patient advocate group pressing for federal research funds and public policies directed toward treatment of, and discovery of a screening test for, ovarian cancer.

I had the privilege of serving on the initial OCRP Scientific Peer Review Committee and have served on the Integration Panel since FY03. My ability to learn a whole new vocabulary of medical research has been facilitated by the extraordinary generosity of the many professionals in the field of gynecologic and oncology research who give of their time to explain their work at advocate-sponsored seminars and conferences."

Ms. Pat Goldman, Integration Panel Member, FY03–FY08



"Since becoming an ovarian cancer survivor, I have met many survivors as well as many women whose lives were taken by this disease. So, when asked if I would like to serve on the 2008 DOD OCRP Career Development panel, I was ecstatic and also hopeful that this program could make a difference. I was not disappointed as I witnessed on our review panel a group of researchers, physicians, and consumer reviewers with the passion of making an impact on this disease. Our panel intensely reviewed submissions in the search for the most promising proposals submitted by young researchers aspiring to pursue independent careers in ovarian cancer research. I applaud OCRP for introducing this unique funding mechanism and playing a crucial role in eliminating this disease."

Debbie Miller, National Ovarian Cancer Coalition, 2008 Peer Review



The OCRP Fills Important Gaps

not addressed by other funding agencies in support of ovarian cancer research. The OCRP vision is adapted yearly to better target funding to the most critical research areas, thus ensuring that the program remains responsive to current needs and future opportunities. A highly flexible management process with proven stewardship, well-qualified people, and productive partnerships has been the key to the OCRP's success.



"The fight against ovarian cancer has made great strides since the inception of the CDMRP Ovarian Cancer Research Program in 1997. We are in an exciting time, marked by an explosion of new areas of success in the laboratory that are translated rapidly to patients, and observations from patients that have stimulated advances in the laboratory. Our progress has drawn the best and brightest into the field of ovarian cancer research, expanding our critical mass of researchers, and the depth and breadth of the work now ongoing.

The DOD's Ovarian Cancer Research Program has been instrumental in identifying and addressing areas of research need, generating a balanced and forward-driving portfolio of prevention, basic biology, biomarker, and translational research. Success of OCRP-funded investigators has been amplified by subsequent funding through other mechanisms. Each funded investigator's research brings the OCRP one step closer to fulfilling the program's vision of eliminating ovarian cancer."

Dr. Elise Kohn, OCRP Integration Panel Chair, FY09-FY10



"DOD funding from the OCRP Pilot grant provided the avenue to my currently funded program in ovarian cancer using the chicken model."

*Dr. Dale Hales, FY05 Pilot
Award recipient*

The OCRP Fills Important Gaps ...By Establishing Shared Resources and Research Tools

From its inception, one of the main goals of the OCRP was to establish shared resources that could be used to study ovarian cancer. This goal was accomplished by funding 16 Program Project awards to support multidisciplinary programs and develop research resources. If these Program

Projects were not funded by the OCRP, it is not certain whether these research resources would be available for researchers today. Four recipients of Program Project awards— M. D. Anderson Cancer Center, Fred Hutchinson Cancer Research Center, Fox Chase

Cancer Research Center, and Brigham and Women's Hospital—were subsequently awarded National Cancer Institute Specialized Program of Research Excellence (SPORE) grants to further support translational research approaches to this disease.

Principal Investigator	Award	Research Resource
Dr. Nicole Urban*	FY97 Program Project	Repository with over 6,000 individually identified ovarian tissue specimens
Dr. Beth Karlan	FY98 Program Project	Human ovarian tissue and clinical database containing ovarian carcinomas (152) and benign ovaries (110)
Dr. Samuel Mok	FY98 Program Project	New biomarkers for early stage ovarian cancer: osteopontin, protease M, and lysophosphatidic acid
Dr. Mary Daly*	FY99 Idea Award	Book, "Ovarian Cancer Risk-reducing Surgery: A Decision Making Resource" (available at no cost to the public)
Dr. Gus Rodriguez and Dr. Patricia Johnson	FY99 Idea Award FY99 New Investigator Award FY01 Program Project	Chicken models of ovarian cancer
Dr. David Bowtell	FY00 Program Project	Multicenter, population-based resource involving collection of linked epidemiologic and clinical data and biospecimens from 2,003 cases and 1,073 matched controls (1,719 questionnaires, 1,694 blood samples, and 1,061 frozen tissue samples) to study ovarian cancer risk factors and biomarkers
Dr. Santo Nicosia	FY01 Program Project	Ovarian cancer tissue repository with more than 600 samples
Dr. Louis Dubeau*	FY03 Idea Development Award	Mouse model with homozygous BRCA1 knockout restricted to ovarian granulosa cells
Dr. Igor Jurisica*	FY04 New Investigator Award	OPHID/I2D – Online databases of known and predicted protein-protein interactions (PPIs) NAViGaTOR – Software package for visualizing and analyzing PPI networks
Dr. Tyler Jacks	FY04 Idea Development Award	Mouse model of ovarian cancer associated with endometriosis
Dr. Patricia Kruk*	FY06 Idea Development Award	Bcl-2 as a urinary biomarker for ovarian cancer
Dr. Robert Kurman	FY01 Program Project	Dualistic model of ovarian cancer that identifies two histological types of tumors – Types I and II Ovarian tumor tissue microarrays – 17 tissue microarrays comprising more than 500 tissues
Dr. Andrew Berchuck*	FY01 Program Project	International Ovarian Cancer Association Consortium (OCAC) currently validating the finding from Dr. Bowtell's Program Project that the +331A allele of the PR gene is significantly associated with protection against endometrioid ovarian cancer
Dr. Georgia Chenevix-Trench	FY05 Idea Development	1,839 ovarian epithelial and theca fibroblast cell samples (675 ovarian cancer cases and 1,164 controls)

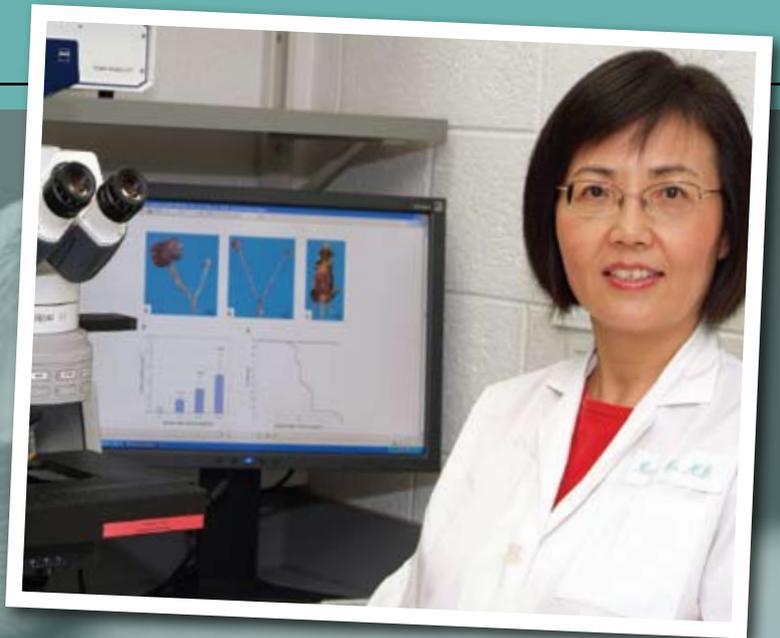


*Pictured at right in order of mention.

The OCRP Fills Important Gaps ...By Investing in Tomorrow's Leaders

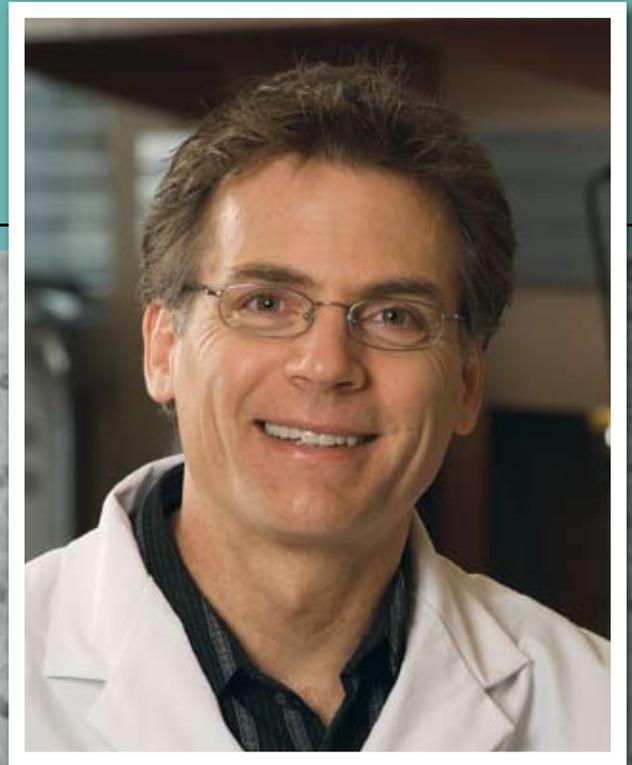
The OCRP is bringing young investigators into the field through several award mechanisms. Since 1998, the OCRP has funded the best and brightest young ovarian cancer researchers with the New Investigator Award. These investigators have made significant contributions, which include testing new therapies for ovarian cancer, discovering new biomarkers that may be used to diagnose the disease in its early stages, and improving the quality of life for women afflicted with the disease. The New Investigator Award has proven to be a very effective mechanism for attracting and retaining new investigators to ovarian cancer research.

With funding from an FY03 New Investigator Award, **Dr. Rong Wu** (pictured), in collaboration with **Dr. Kathleen R. Cho** from the University of Michigan, established a novel mouse model of endometrioid carcinoma induced by conditional inactivation of tumor suppressor genes (*Apc* and *Pten*) in the mouse ovarian surface epithelium. The tumors were grossly apparent within 6 weeks of the induction, and they resembled human tumors morphologically and genetically. The research team continues to develop this model as a tool for preclinical testing of novel therapeutics targeting *Apc* and *Pten* signal transduction pathways.



Eliciting Autoimmunity to Ovarian Tumors in Mice by Genetic Disruption of T-Cell Tolerance Mechanisms

Dr. Brad Nelson from the British Columbia Cancer Agency received an FY00 New Investigator Award to study how ovarian tumors evade the immune system, leading to metastatic disease in patients with intact immune systems. Dr. Nelson developed a novel mouse model that allows analysis of CD4+ and CD8+ T-cell responses to ovarian tumors over time and after various immune interventions. Tumors within this mouse model express a modified version of the neu oncogene, commonly expressed in ovarian tumors. Dr. Nelson found that CD8+ T cells specific for the modified neu antigen were highly responsive to ovarian tumors, causing regression of advanced disease in 75% of cases, without the need for surgery or chemotherapy. Dr. Nelson also found that deletion of a negative regulator, Cbl-b, from CD8+ T cells resulted in increased T-cell proliferation and tumor regression, thus revealing a potential target for improving T-cell therapy against ovarian cancer. More recently, Dr. Nelson received an FY08 Idea Award for his proposal entitled “Control of Disease Recurrence by Tumor-Infiltrating T Cells in Ovarian Cancer.” This research will be the first to explore the hypothesis that chemotherapy induces mutations in the tumor genome, resulting in new tumor antigens which, in turn, trigger T-cell responses. There is good evidence that such T-cell responses may delay or prevent tumor recurrence in many patients. The identification of these T-cell-stimulating antigens could lead to the development of improved immunotherapy for ovarian cancer.



The OCRP Fills Important Gaps...By

Supporting Training

With the Historically Black Colleges and Universities/Minority Institutions (HBCU/MI) Fellowship Award offered in FY07, the OCRP supports mentored training and research experiences of promising HBCU/MI scientists. This support greatly helps to prepare these future researchers, whose efforts to conduct ovarian cancer research often are hampered by a lack of training and resources, for productive careers in ovarian cancer research.

Synergistic Effects of CXCR4 and FAK in Ovarian Cancer Progression and Metastases

Dr. Edna Mora of the University of Puerto Rico received an FY07 HBCU/MI Fellowship to train with Dr. Anil Sood at the M. D. Anderson Cancer Center. Dr. Mora's research training will focus on how the chemokine receptor 4 axis (CXCR4/CXCL12) activates focal adhesion kinase (FAK) to promote tumor progression and metastases in ovarian cancer.

Association of the UGTB17 Gene Deletion Polymorphism and the Incidence of Ovarian Cancer and Ethnicity

Dr. Delores Grant of North Carolina Central University was awarded an FY07 HBCU/MI Fellowship to work under the mentorship of Dr. Joellen Schildkraut at Duke University Medical Center. Dr. Grant will determine the association and linkage of the polymorphisms of the UGT2B, androgen receptor (AR), and progesterone receptor (PR) genes to test the hypothesis that changes in the DNA sequence variants of the UGT2B, AR, and PR genes are associated with increased susceptibility to ovarian cancer.

The Career Development Award, a new award mechanism offered by the OCRP in FY08, helps to support research training opportunities for investigators in the early stages of their careers by providing the funding and experience necessary to pursue an independent career at the forefront of ovarian cancer research.



The OCRP Fills Important Gaps

...By Supporting Innovative Research

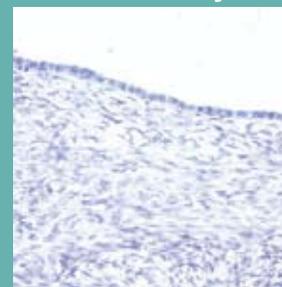
Through its various award mechanisms, the OCRP has always encouraged high-impact, highly innovative research. Two particularly successful awards have been the Idea Development Award, offered since FY02, and the Pilot Award, offered in FY05. Through these awards, the OCRP has funded innovative research targeting areas that may have the greatest impact on the field of ovarian cancer research.



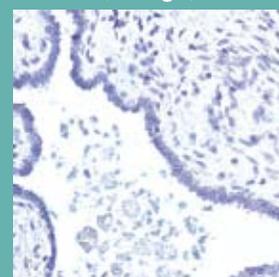
Dr. Honami Naora of the M. D. Anderson Cancer Center hypothesized that ovarian surface epithelium has an embryonic-like phenotype resembling that of hematopoietic progenitor cells and, therefore, could be highly susceptible to the effects of aberrant homeobox gene activation. With funding from an FY05 Idea Development Award, Dr. Naora's team focused on the DLX4/BP1 homeobox gene that is located on chromosome 17q in a

region whose amplification correlates with poor prognosis in ovarian cancer. These researchers found that DLX4 was not expressed in normal ovary and cystadenomas, but its expression in ovarian carcinomas was significantly associated with high tumor grade and advanced disease stage. Imaging of mice bearing intraperitoneal ovarian tumors revealed that DLX4 overexpression substantially increased tumor burden and tumor vascularization. Furthermore, DLX4 induced expression of vascular endothelial growth factor (VEGF) as well as intracellular and secreted isoforms of fibroblast growth factor-2. These findings show a novel proangiogenic, growth stimulatory mechanism for a homeobox gene in promoting ovarian tumorigenesis and suggest new therapeutic targets and strategies for ovarian cancer. Dr. Naora also received an FY02 Idea Development Award to explore the molecular pathways underlying the histogenesis and heterogeneity of epithelial ovarian cancer tumors.

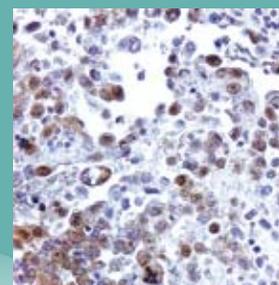
normal ovary



*ovarian cystadenoma
(benign)*



*high-grade ovarian
carcinoma*

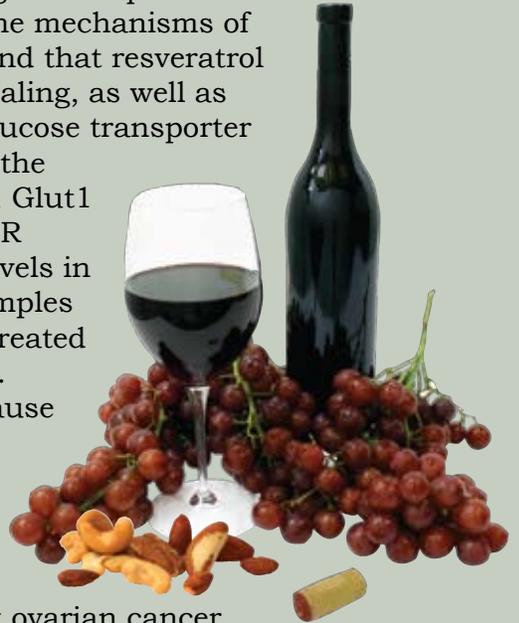




Dr. Rebecca Liu of the University of Michigan, recipient of an FY05 Idea Development Award, is studying the anti-cancer properties of resveratrol, a plant compound present in grapes, nuts, and red wine. Dr. Liu's team found that resveratrol induced autophagocytic cell death in ovarian cancer cells by inhibiting glucose uptake.

The researchers studied the mechanisms of resveratrol action and found that resveratrol inhibited AKT/mTOR signaling, as well as the translocation of the glucose transporter Glut1 from the cytosol to the membrane. Interestingly, Glut1 and phosphorylated mTOR were expressed at high levels in ovarian cancer tissue samples from patients who were treated with carboplatin and paclitaxel.

These results suggest that because resveratrol induces cell death through a mechanism distinct from apoptosis, resveratrol treatment may provide a therapeutic advantage in the management of chemoresistant ovarian cancer.



Dr. Patricia Kruk of the University of South Florida found that over 70% of ovarian cancer patients had detectable levels of the protein Bcl-2 in their urine samples. These preliminary findings led to Dr. Kruk's FY06 Idea Development Award that focuses on whether Bcl-2 can be used as a urinary biomarker for ovarian cancer. Early results indicate that elevated urinary Bcl-2 levels are detectable by enzyme-linked immunosorbent assay.

Dr. Kruk also was the recipient of an FY99 New Investigator Award, and she was one of the investigators who participated in Dr. Santo Nicosia's FY01 Program Project Award.

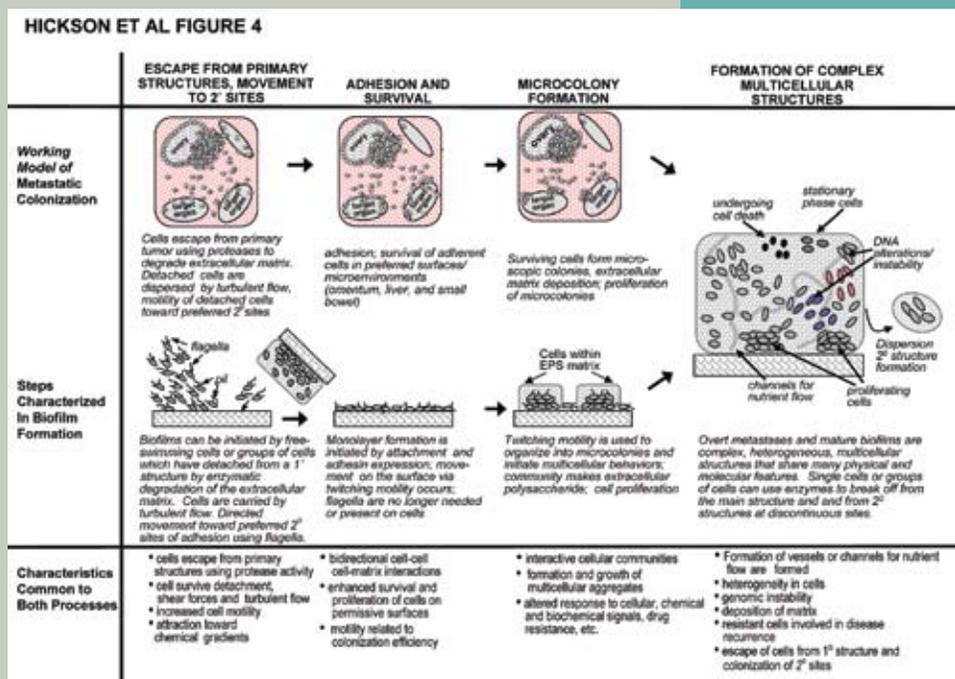
The OCRP Fills Important Gaps ...By Accelerating Discoveries

"...The new paradigms session at the AACR/MRS meeting...was extremely well received. I presented our quorum-sensing hypothesis in concert with talks by Matt Parsek and Mike Federle, who are leaders in the fields of quorum sensing and biofilms...It was truly ground breaking and caught a lot of peoples' interest. I would never have had this opportunity without DOD ovarian cancer funding. I am totally jazzed and determined to keep moving forward on this new paradigm."

Dr. Carrie Rinker-Schaeffer, FY05 Pilot Award recipient



Dr. Carrie Rinker-Schaeffer's pioneering studies are the first to investigate the quorum-sensing behavior of bacteria as potential processes that regulate metastases in ovarian cancer. Quorum sensing is a process of cell-cell communication that bacteria use to control gene expression in response to fluctuations in cell population density. In quorum sensing, a critical number of cells, rather than the entire population of bacterial cells, carry out processes in synchrony. A metastasis expert from the University of Chicago, Dr. Rinker-Schaeffer is testing the hypothesis that groups of ovarian cancer cells can communicate through quorum-sensing-like mechanisms and through gene expression confer cellular changes required for metastatic colonization. By looking at cancer metastasis from a new perspective, these studies challenge traditional hypotheses and may provide insight into novel molecular mechanisms underlying the metastatic process.



Hickson J, Yamada SD, Berger J, et al. 2008. Societal interactions in ovarian cancer metastasis: A quorum-sensing hypothesis. *Clin Exp Metastasis* [Epub ahead of print].

The OCRP Fills Important Gaps ...By Drawing from Diverse Disciplines

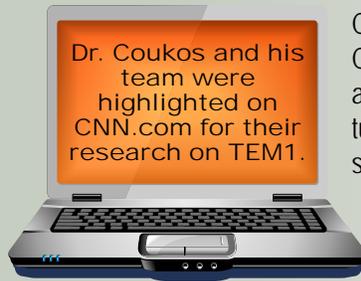


Dr. Touradj Solouki of the University of Maine is a chemist with expertise in mass spectrometry. With funding from an FY06 Idea Development Award, Dr. Solouki and his collaborators at the Pine Street Foundation (Michael McCulloch, epidemiologist) are using their knowledge to develop an innovative approach for early detection of ovarian cancer. They hypothesize that exhaled breath condensate is a valuable source of biomarkers that can distinguish women with epithelial ovarian cancer from

both healthy controls and women with endometriosis or polycystic ovarian syndrome. The research team is exploring this hypothesis by using chemical methods (gas chromatography/Fourier transform ion cyclotron resonance mass spectrometry [GC/FT-ICR MS] in the University of Maine's chemistry laboratory) and biological methods (trained dogs in Pine Street Foundation's California laboratory). These studies may result in the detection of ovarian cancer at an earlier stage than currently detected through CA-125 and ultrasound.



Dr. George Coukos of the University of Pennsylvania, recipient of an FY05 Idea Development Award, is targeting tumor vasculature cells to suppress ovarian cancer growth. Dr. Coukos' team found that the antiangiogenesis drug SU5416 in combination with low-dose paclitaxel provided therapeutic advantage in tumors with low levels of VEGF. The researchers are also targeting human tumor vascular cells through tumor endothelial marker 1 (TEM1), and they have developed innovative in vivo models to



Chungseng Li, a postdoctoral fellow in the laboratory of George Coukos, was highlighted on CNN.com for his research on TEM1, a gene overexpressed in the blood vessels feeding some ovarian tumors. Overexpression of this gene always correlates with decreased survival, making it a possible target for screening and gene therapy.

<http://www.cnn.com/2008/HEALTH/conditions/09/23/ovarian.cancer.marker/index.html>

test human (h)TEM1 targeting tools in the mouse. Finally, Dr. Coukos' team validated the tumor vascular markers adlcan and DR6 as therapeutic targets. They found high levels of adlcan in ovarian cancers but low levels in normal tissues. Furthermore, adlcan protein was detected in tumor, ascites, and serum of ovarian cancer patients but not in normal serum. DR6 protein was highly

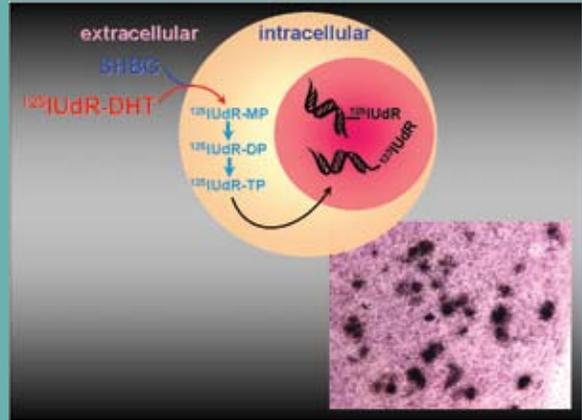
expressed in the vasculature of solid tumors and was detected in the serum of patients with ovarian cancer at higher levels than found in individuals without cancer. These results offer new strategies for targeting tumor vasculature and designing rational combinatorial therapy to treat ovarian cancer.



The OCRP Fills Important Gaps ...By Improving Treatment



Dr. Janina Baranowska-Kortylewicz of the University of Nebraska, utilizing funds from an FY03 Idea Development Award, has discovered that ovarian cancer tumors with a higher fraction of cells in cell cycle S-phase are considered more difficult to treat and are considered to be predictive of poor prognosis.



New classes of radiopharmaceutical drugs were developed that are ovarian cancer-specific and preferentially kill aggressively growing tumors. The targeted delivery system uses two agents, dihydrotestosterone as the receptor-based tumor-seeking moiety and the cell-cycle-dependent drug 5-radioiodo-2'deoxyuridine. There is higher uptake of this drug combination into the DNA of tumor cells that are both androgen receptor-positive and have higher S phase fractions. Both in vitro and in vivo studies have confirmed the efficacy of this new class of drugs.



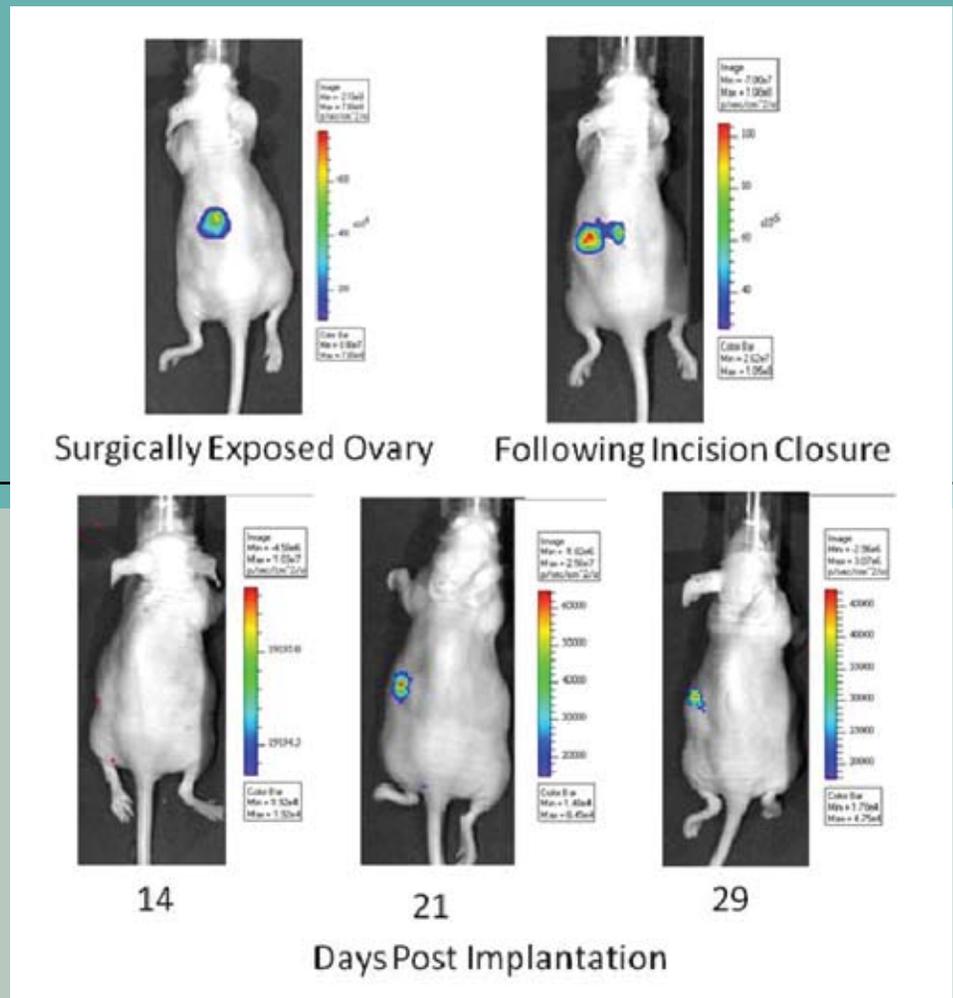
Dr. Francis Markland of the Keck School of Medicine at the University of Southern California is studying snake venom as a potential ovarian cancer therapeutic. With funding from an FY06 Idea Development Award, Dr. Markland's laboratory has shown that contortrostatin (CN), the protein isolated from snake venom, has potent antitumor activity since it directly inhibits cancer cell growth and inhibits angiogenesis. The researchers have also produced vicrostatin (VN), a synthetic variant of CN, and found it to be as active as CN. Both CN and VN exert their antitumor activities by binding to integrins, which are cell surface proteins important in cell-to-environment com-

munications and in cell migration. Dr. Markland's laboratory is optimizing the production of recombinant VN, and the researchers are testing its efficacy either alone or in combination with cytotoxic chemotherapy as a treatment for ovarian cancer. The researchers are also testing the ability of VN as an imaging agent for integrin-positive epithelial ovarian cancer.



Development of an Orthotopic, Xenograft Ovarian Cancer Model

Human cancer cells are injected into the surgically exposed ovary of middle-age Nu/Nu mice. The luciferase-transduced cancer cells are mixed with luciferin and locally injected into the left ovary. The upper left panel shows the exposed ovary with injected luciferase-transduced cells while the upper right panel shows the luciferase-transduced cells after closing the incision. Lower panels show viability in mice recovering from the surgery. Persistence and viability of cells up to 29 days are shown (from left to right: 14, 21, and 29 days). At Day 14, the founding population of cancer cells was below a detectable limit, but on subsequent days, as the tumor grows, luciferase levels are detectable. Further study of the growth of orthotopic ovarian cancer is in progress in combination with the imaging potential of VN, the recombinant version of the snake venom protein contortrostatin.



The OCRP Fills Important Gaps...By Supporting Collaboration and Translational Research

For two out of three ovarian cancer patients, the difficult reality to be faced is that each woman will be diagnosed at an advanced stage of disease and face 5-year survival rates of less than 30%. In light of this, the OCRP understands the critical and urgent need to accelerate new discoveries and translate these to patients. In FY07, the OCRP offered the Translational Research Partnership Award, which is designed to fund research collaboration between a laboratory scientist and a clinician in an effort to drive a discovery regarding ovarian cancer forward into clinical application. These investigators must demonstrate a true partnership through the reciprocal flow of ideas and information from bench to clinic.



As FY07 recipients of the Translational Research Partnership Award, **Drs. Kathleen Cho** (pictured) and **Alnawaz Rehemtulla** from the University of Michigan are using the *ApcloxP/loxP; PTENloxP/loxP* mouse model of ovarian endometrioid adenocarcinoma, coupled with molecular imaging technologies, to identify novel therapeutic targets for ovarian cancer. This project has the potential to greatly impact patients by providing the tools necessary for developing “personalized” therapeutics for patients based on their tumor’s particular gene expression.

The mouse model used in this research was developed by Dr. Cho in collaboration with Dr. Rong Wu under Dr. Wu’s DOD FY03 New Investigator Award.



Dr. Michael Morse of Duke University Medical Center, an FY07 Translational Research Partnership Award recipient, is collaborating with **Dr. Ramila Philip** of Immunotope, Inc. to design a tumor vaccine that will specifically target chemotherapy-resistant ovarian cancer. As the majority of ovarian cancer patients are diagnosed with advanced disease, 70%–90% of these patients unfortunately suffer a relapse and die due to the development of chemotherapy-resistant tumors. Therefore, the research of Drs. Morse and Philip could have a profound effect on ovarian cancer patient survival. Furthermore, this line of therapy has limited side effects, thus improving the quality of life for these patients while conferring a long-term immunity to recurrence and metastasis.



...the OCRP vision
is adapted yearly
to better target
funding to the
most critical
research areas

The OCRP Fills Important Gaps

...By Improving Quality of Life



Dr. Mary Daly of Fox Chase Cancer Center has been studying quality of life (QOL) issues in women undergoing prophylactic oophorectomy. Many women at high risk for ovarian cancer often elect surgical removal of the ovaries as a preventive measure. With funding from an OCRP FY99 Idea Development Award, Dr. Daly's team compared populations of women matched in age, race, education, marital status, and BRCA gene mutation status, and recorded whether they did or did not proceed with prophylactic surgery. Managing surgically induced short-term menopause-like symptoms is an important area of clinical intervention. However, despite the short-term symptoms of increased hot flashes and night/cold sweats, decreased physical and social functioning, and decreased sexual activity and pleasure, women undergoing prophylactic oophorectomies reported extremely high levels of satisfaction and confidence in their decisions.



Dr. Nancy Avis received funding through an FY00 New Investigator Award to study QOL among women with ovarian cancer. The primary objective of the Wake Forest University researcher was to identify those issues of greatest concern to women in the three treatment stages: newly diagnosed with ovarian cancer, in treatment, and post-treatment. Dr. Avis' secondary objective was to assess changes in QOL across the different stages of care. Questionnaires were administered to participants after diagnosis and prior to (baseline), during, and following chemotherapy, and after any recurrence. Overall, QOL and physical problems were most pronounced at baseline and improved over time during treatment. Social support and absence of comorbidities were significantly associated with better QOL. The emotional well-being of patients improved faster for those with higher educational attainment, although similar emotional well-being scores were reported after 2 years for all women regardless of level of education. Last, the researcher found that interventions to improve QOL among women with ovarian cancer would be most effective when made available immediately following diagnosis.

Dr. Sandra Zakowski of the Rosalind Franklin University of Medicine and Science, recipient of an FY00 New Investigator Award, is attempting to improve quality of life for ovarian cancer patients and their partners through emotional expression in journal writings. Subjects in the intervention group were asked to write about their deepest thoughts and feelings related to their cancer experience for 20 minutes each day on 3 consecutive days. In contrast, the control group was asked to write about trivial, nonemotional assigned topics. Follow-up assessments were performed for up to 9 months post-intervention. Promising preliminary results suggest that cancer patients, especially those with low scores for neuroticism and/or high scores for extraversion, benefitted from the writing intervention. Those patients with little interpersonal support also benefitted from the intervention. Overall, this study provided valuable information about the relations between emotional expression, personality, and psychological adjustment in cancer patients.



...the OCRP
understands
the **critical** and
urgent need to
accelerate new
discoveries and **translate**
these to
patients.

OCRP Research Highlights

NOTABLE RESEARCH ADVANCES

Shown that vitamin A analogs in combination with progestins stimulate selective apoptosis of ovarian cancer cell lines in vitro.

Found that ovarian granulosa cells not only control the menstrual cycle but also control ovarian tumor development.

Developed alpha-particle emitters as radiotherapeutics for advanced ovarian cancer.

Found that three HOX genes, HOXA9, HOXA10, and HOXA11, can be used as biomarkers to detect ovarian cancer.

Shown that squalamine is antiangiogenic and enhances the cytotoxic effect of cisplatin on ovarian cancer cells.

Found that the copper uptake protein CTR1 regulates cellular uptake of platinum drugs, which is important for overcoming drug resistance.

Discovered that poly-l-glutamate conjugated paclitaxel and hyaluronic acid conjugated paclitaxel can be used to overcome paclitaxel resistance.

Discovered epithelial cell adhesion molecule as a possible biomarker for ovarian cancer.

Generated a chicken model that can be used to study ovarian cancer.

Discovered that the gene TEM1 is overexpressed in the blood vessels of some ovarian tumors. Targeting this gene may lead to improved tumor visualization as well as ovarian cancer screening and treatment.



ONGOING RESEARCH

Investigating the levels of different human endogenous retroviruses as diagnostic and prognostic indicators of ovarian cancer.

Developing novel early detection methods for epithelial ovarian cancer based on sensitive optical techniques that recognize the chemical composition of ovarian cancer.

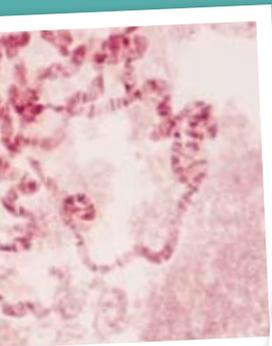
Identifying and characterizing ovarian carcinoma stem cells using the stem cell marker aldehyde dehydrogenase.

Examining the historical association between the incidence of mumps (parotitis) and ovarian cancer, a potential new paradigm that may offer new avenues of prevention.

Developing bioresponsive nanoparticles as MRI molecular probes for early detection.

Evaluating if anti-ovarian auto-antibodies predict ovarian cancer (hen model).

Silencing mesothelin (plasma membrane antigen, highly expressed in ovarian cancer) by using short interfering RNA.





For more information, contact
<http://cdmrp.army.mil/ocrp>
or
Ms. Gail Whitehead,
Public Affairs Coordinator
Gail.Whitehead@amedd.army.mil
(301) 619-7783

