



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 CDMRP has grown to encompass multiple targeted programs and has received over \$8.22 billion in appropriations from its inception through fiscal year 2014 (FY14). 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 with specific guidance from Congress.

Application Review Process

The CDMRP uses a two-tier review process for application evaluation which is critical to ensuring that each of the research program portfolios reflects not only the most meritorious science, but also the most programmatically relevant research. This review process, adopted from the recommendations set forth in 1993 by the National Academy of Science's Institute of Medicine, involves dynamic interactions between scientists and disease survivors at both tiers. The first tier of application evaluation is a scientific peer review of applications measured against established criteria for determining scientific merit. The second tier is a programmatic review, conducted by the Integration Panel (IP) which is composed of leading scientists, clinicians, and disease survivors. The IP compares applications to each other and makes recommendations for funding based on scientific merit, potential impact, relevance to program goals, and portfolio composition.

For most award mechanisms (i.e., funding opportunities), a pre-application screening process is included in order to focus the resources of the applicants, reviewers, and program staff on research that best meets the intent of the award mechanism. Favorably reviewed pre-applications are then invited for submission as full applications, which are evaluated using the two-tier review process.

History of the DoD OCRP

Since its inception in 1997 and over the past 17 years, the DoD OCRP has had a critical role in supporting high-impact, innovative research to understand, prevent, detect, diagnose, and treat ovarian cancer. In concert with the OCRP's accomplishments, the dedicated efforts of ovarian cancer advocates to increase public awareness of and research funding for ovarian cancer have resulted in congressional appropriations totaling over \$236 million (M) through FY14. As a leader in funding ovarian cancer research, the DoD OCRP invests in high-impact, cutting-edge research that fills unmet needs and pushes the field of ovarian cancer forward to eliminate this disease.

To be responsive to the needs of the ovarian cancer community, the OCRP vision is adapted yearly. The OCRP IP meets annually to deliberate the issues and concerns unique to ovarian cancer, and to establish a program strategy by considering research gaps, critical research areas, and the needs of the ovarian cancer community. The OCRP analyzes the funding landscape by comparing research portfolios and award mechanisms from over 70 federal and non-federal agencies throughout the world. The OCRP then sets its program priorities, develops award mechanisms, and establishes an investment strategy to target the most critical needs along the pipeline from basic to translational to clinical research. The OCRP's annual investment strategy and associated award mechanisms provide the framework and direction necessary to most effectively invest the congressional appropriation in ovarian cancer research.

Did you know?

- According to the World Health Organization, approximately 238,700 women were diagnosed with ovarian cancer worldwide in 2012, and 151,900 died of the disease.
- Ovarian cancer is the deadliest female reproductive cancer in the U.S.; approximately 14,270 women will die from the disease in 2014 (per the American Cancer Society).

Key Initiatives of the DoD OCRP

The OCRP established key initiatives to encourage researchers to focus on those areas of research with the greatest need.

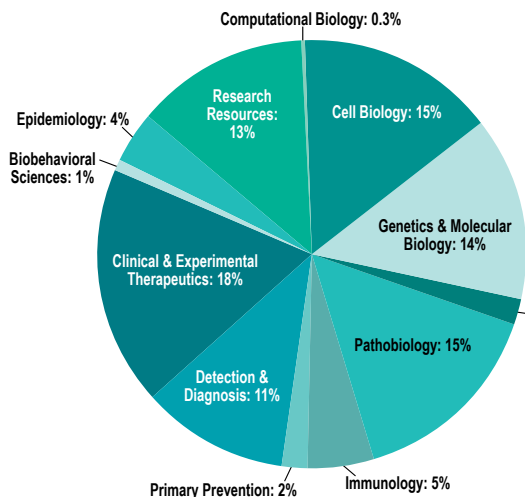
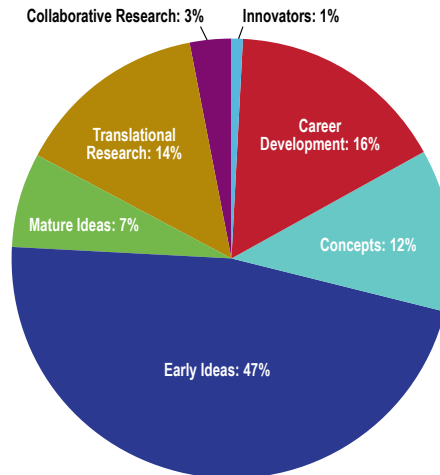
- Understand precursor lesion/stem cell, microenvironment, and pathogenesis/progression of all types of ovarian cancer, including rare subtypes
- Develop or improve performance and reliability of screening, diagnostic approaches, and treatment
- Develop and validate models to study initiation and progression of ovarian cancer
- Address issues in primary prevention and survivorship
- Investigate tumor response to therapy including tumor survival, dormancy, cell death, clonal evolution, and tumor heterogeneity
- Enhance the pool of ovarian cancer scientists

Did you know?

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

A total of 314 awards were made through FY13, and this program booklet reports on some of the recent advancements accomplished in the DoD OCRP.

OCR P FY97–FY13
Development of Ideas
(Per number of awards)



OCR P FY97–FY13
Portfolio Categorized
by Research Area
(Per number of awards)

VISION

Eliminate ovarian cancer.

MISSION

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

Integration Panel Members

Molly Brewer, D.V.M., M.D., M.S.
FY14 Chair

Carole and Ray Neag Comprehensive
Cancer Center, University of
Connecticut

Deborah Armstrong, M.D.
Johns Hopkins University

Edward Brown, Ph.D.
University of Rochester

Robert Coleman, M.D., FACOG, FACS
University of Texas MD Anderson
Cancer Center

Annie Ellis
Ovarian Cancer National Alliance

John H. Farley, M.D., COL (Ret), MC
Creighton University School of
Medicine at St. Joseph's Hospital and
Medical Center

Judi Gordon
SHARE

Linda Malkas, Ph.D.
Beckman Research Institute of City
of Hope

Brad Nelson, Ph.D.
British Columbia Cancer Agency

Alexander Nikitin, M.D., Ph.D.
Cornell University

William Rodgers, M.D., Ph.D.
New York Hospital Queens

M. Sharon Stack, Ph.D.
University of Notre Dame

Katrina Trivers, Ph.D., M.S.P.H.
Centers for Disease Control and
Prevention

Shannon Walker, M.D.
Granulosa Tumor Foundation

Strategic Partnerships

The significant impact of the DoD OCRP can be attributed to the collective wisdom and synergistic efforts of many talented and dedicated ovarian cancer survivors (consumers), clinicians, scientists, and the military. This partnership brings together stakeholders that typically might not collaborate, to help shape the OCRP and accelerate research to accomplish the OCRP vision of eliminating ovarian cancer. As partners in vision setting, peer review, and programmatic review, they have shaped the OCRP by focusing on research that reflects the needs of survivors and their families, as well as the clinicians who treat them.

- More than 750 scientists and ovarian cancer consumers have contributed their expertise to the OCRP's two-tier application review process.
- Consumer advocates and scientists participate as equal voting members during both peer and programmatic review of proposals.
- Ovarian cancer survivor participation is critical to the OCRP – they challenge the scientists and clinicians to expeditiously find innovative solutions.
- Ovarian cancer survivors from over 65 advocacy organizations and over 25 states have played a pivotal role in the establishment and impact of the OCRP.
- Ovarian cancer consumers bring their firsthand experiences and consumer needs to the table, working together with scientists to define the OCRP's vision and research priorities.
- Ovarian cancer consumers serve as a voice for all survivors, providing a different perspective and helping scientists understand how the research will impact their quality of life.
- Ovarian cancer survivors are integrally involved in consortia that are conducting research on predictors of disease outcomes, particularly in ovarian cancer patients who are long-term survivors.



“Serving on the Integration Panel has been such an honor. The level of knowledge and dedication to ending this disease continues to encourage me. I have hope that one day, the answer will be found.”

*~Shannon Walker, M.D.,
Granulosa Tumor Foundation,
IP Member*



“It is always a great pleasure and privilege to serve as a DoD OCRP grant reviewer. The members of grant review panels represent a unique blend of scientific and consumer reviewers who are deeply committed to a consistent and thorough grant review process. As a reviewer, it is exciting and rewarding to participate in a program that supports scientifically sound and highly innovative research proposals with the promise to drive the field forward and positively impact patients.”

**~Patricia Kruk, Ph.D., University of South Florida,
Peer Reviewer**

“Serving as a Consumer Reviewer for the Ovarian Cancer Research Program for the past two years has been an honor as well as a challenging pleasure. As a survivor, it is extremely rewarding to see the breadth of applications focused solely on ovarian cancer research. No longer is ovarian cancer a silent killer. These brave researchers are moving into the forefront of the medical world by working on viable ways to detect and slow the disease with targeted and direct treatments. The DoD Ovarian Cancer Research Program review process gave me incredible hope for all my sisters who suffer from this devastating disease. Often I had to tie my ankles together to keep from jumping up and down from excitement throughout my reading of the applications. It was thrilling to read of so much original scientific research. This experience has opened my eyes to a world of hope for this disease.”



**~Benita Koman, Ovarian Cancer National Alliance,
Consumer Peer Reviewer**



“The DoD OCRP is one of the largest ovarian cancer research funders. It is an honor to serve on the IP with this dedicated group of scientists and advocates who are dedicated to improving outcomes for women with ovarian cancer. We are funding new research to better understand ovarian cancer, to improve treatment, to reduce side effects and most importantly to train the next generation of ovarian cancer researchers.”

~Molly A. Brewer, DVM, MD, MS, FY14 IP Chair

The DoD OCRP – Continuing to Move the Field Forward

ADDRESSING UNMET NEEDS BY ESTABLISHING PRIORITIES, CRAFTING NOVEL AWARD MECHANISMS, AND SUPPORTING CUTTING-EDGE RESEARCH

In striving to achieve the vision of eliminating ovarian cancer, the DoD OCRP Integration Panel designed an investment strategy for FY14 that continues to emphasize high-impact translational research, innovation, and training for talented, young investigators in order to unravel the increasing complexity of ovarian cancer.



Elizabeth Swisher, M.D.
University of Washington

FY07 Translational Research Partnership, FY12 Pilot, and Synergistic Translational Leverage Awards

“The DoD OCRP fills a funding niche not provided by the NIH; that is, they provide reasonable size awards for high-risk, high-reward, translationally relevant research in ovarian cancer. As a physician scientist, this funding has been essential to my career in translational research.”

INNOVATION, HIGH-IMPACT

Pilot Award

- FY14 OCRP continues to focus on innovative, high-risk/high-reward research.
- Research may lead to critical discoveries or major advancements that will provide new paradigms, insights, technologies, or applications to prevent ovarian cancer or improve the treatment of individuals with this disease.
- Award includes an option of a *nested Teal Postdoctoral Scholar* to mentor postgraduate trainees in basic and clinical ovarian cancer research.

ACCELERATING PROMISING RESEARCH

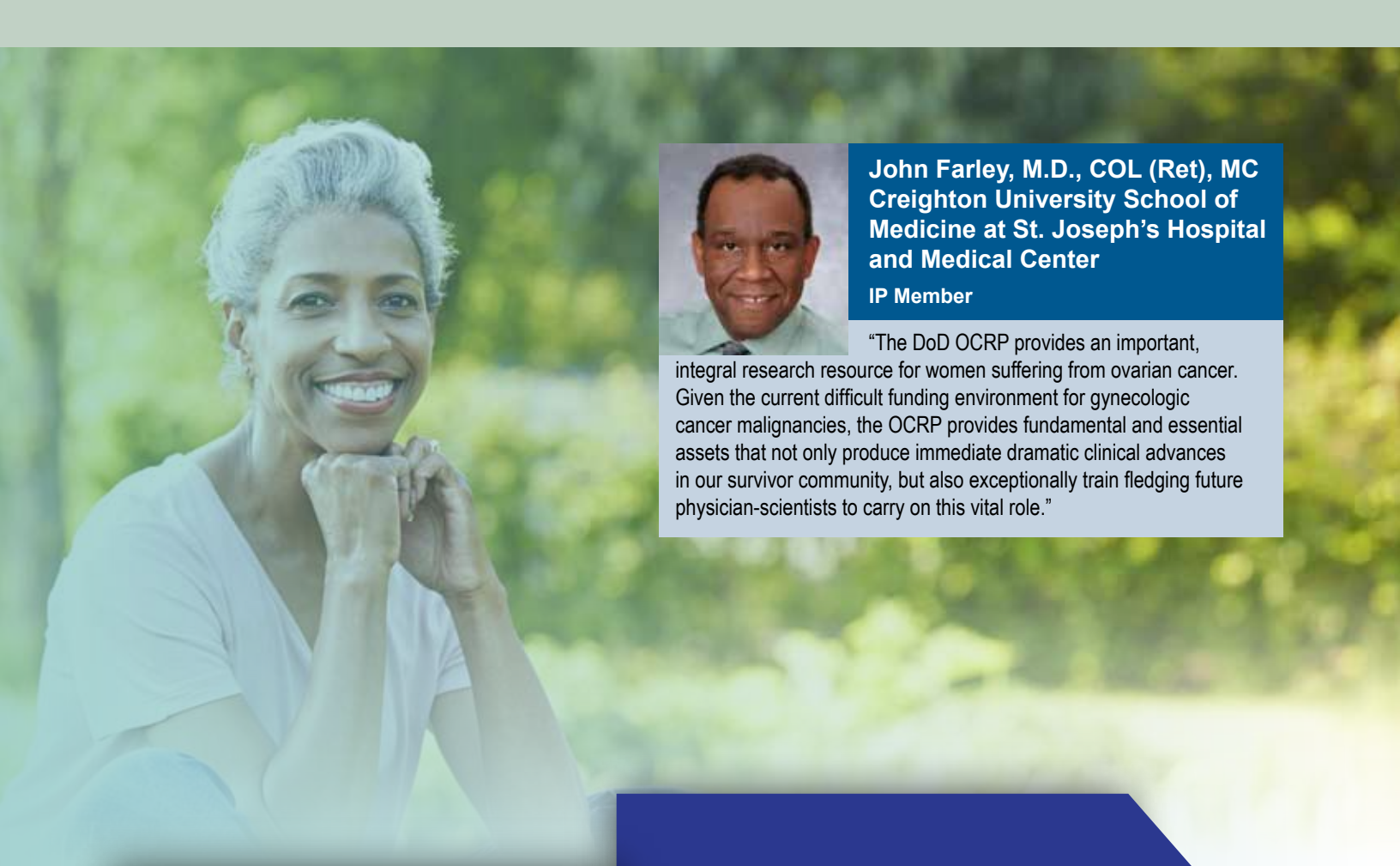
Investigator-Initiated Research Award

- FY14 OCRP offers this award mechanism to support research that will significantly impact ovarian cancer research and/or patient care.
- May focus on any phase of research from basic through translational research.
- Award supports projects with strong preliminary data relevant to ovarian cancer.

CULTIVATING TALENTED INVESTIGATORS COMMITTED TO OVARIAN CANCER RESEARCH

Ovarian Cancer Academy Awards

- OCRP continues to build a critical mass of dedicated, career ovarian cancer researchers through its Ovarian Cancer Academy Awards.
- Ovarian Cancer Academy (Early Career Investigators, Designated Mentors, and Dean) is a unique, interactive virtual academy providing intensive mentoring, national networking, and a peer group for junior faculty.
- FY14 award mechanisms solicit additional Early-Career Investigators as well as the Academy Leadership (Dean and Assistant Dean) for this highly successful Academy.



John Farley, M.D., COL (Ret), MC Creighton University School of Medicine at St. Joseph's Hospital and Medical Center

IP Member

“The DoD OCRP provides an important, integral research resource for women suffering from ovarian cancer. Given the current difficult funding environment for gynecologic cancer malignancies, the OCRP provides fundamental and essential assets that not only produce immediate dramatic clinical advances in our survivor community, but also exceptionally train fledging future physician-scientists to carry on this vital role.”

FACILITATING COLLABORATIVE PARTNERSHIPS

- OCRP recognizes that research collaborations are important in investigating the increasing complexity of ovarian cancer, and has developed “Team Science” award mechanisms that bring together the most talented scientists from different disciplines and organizations to solve a problem.

Outcomes Consortium Award

- FY14 OCRP offers stage 2 of the Outcomes Consortium Award to bring together the most talented scientists and ovarian cancer survivors to solve a problem.
- This award specifically focuses on identifying and understanding predictors of disease outcomes in ovarian cancer patients.
- Research focus is on predictors of disease outcomes, particularly identifying what is unique to long-term survivors (at least 10 years from initial diagnosis) as compared to short-term survivors.

TRANSITIONING TO PATIENT CARE

Clinical Translational Leverage Award

- FY14 OCRP continues to offer this award mechanism to accelerate successful laboratory results to the clinical setting.
- For FY14, this award mechanism is dual-hatted to support early-phase clinical trials or correlative studies (both retrospective and prospective) to investigate high-impact research ideas or unmet needs in ovarian cancer.
- Award requires leveraging existing human-based ovarian cancer resources.

Teal Innovator

The OCRP Teal Innovator Award supports a highly recognized, visionary individual with the funding and the freedom to focus his/her creativity, innovation, and leadership on high-risk ideas that could significantly impact ovarian cancer research or patient care.

FY13 Teal Innovator – Reversing a Cancer Switch **Stephen B. Baylin, M.D., Johns Hopkins University**

One of the ways that tumors may form and grow is through epigenetic changes, changes to the structure of the DNA but not its content. These changes to the structure are normal in small amounts, but in tumors the amount and location of modifications may be increased and occur in important parts of the genome. This leads to the over- or underexpression of genes in ways that are similar to DNA mutations; however, unlike DNA mutations, epigenetic changes have the potential to be reversible. Reversing the epigenetic changes in a cancer cell may reprogram it to a more “normal” state, halting progression of the tumor and ideally leading to its reversal. Dr. Stephen Baylin, recommended for funding as the FY13 Teal Innovator, plans to pursue a deeper understanding of the epigenetic changes that occur in ovarian cancer and the potential for reversal, noting “nothing needs a new approach more than ovarian cancer.”

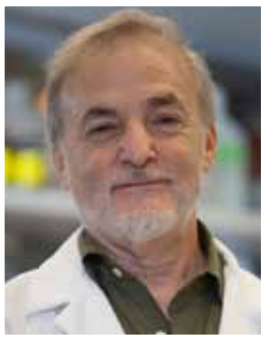
Epigenetic therapies are under development for other diseases, and Dr. Baylin has compiled a team of experts in related fields to help him make the strongest advance in this area. He will utilize his ongoing collaboration with Dr. Peter Jones at the University of Southern California and Dr. Cynthia Zahnow at Johns Hopkins to strengthen the experience in epigenetics, and he will leverage his collaboration with Dr. Dennis Slamon at the University of California, Los Angeles to facilitate drug sensitivity profiles for ovarian cancer cell lines. Another collaborator at Johns Hopkins, Dr. Drew Pardoll, is an immunology expert who is working with Dr. Baylin and, in particular his postdoctoral fellow, Dr. Katherine Chiappinelli. The aim is to use epigenetic therapy to sensitize tumor cells to immunotherapies in order to “hugely impact management of the disease...at least prolonging the lifespan of women with advanced ovarian cancer and markedly changing the outcome of women with the disease.” This impact includes potential leveraging of any positive results to clinical trials through his collaboration with Dr. Slamon, who has a successful history of developing immunotherapies (most notably Herceptin® for breast cancer treatment).

Dr. Baylin looks forward to sharing his “true excitement” in applying his epigenetic focus on ovarian cancer with the patient and research communities, saying “we are dearly excited to have gotten the opportunity to do this.”

Update from FY11 Teal Innovator **Garry P. Nolan, Ph.D., Stanford University**

My lab is focused on single-cell approaches based on the premise that individual cells within the same population may differ dramatically, and these differences can have important consequences for the health and function of the entire tumor population. We need to have very rigorous approaches to dismantle high-grade serous ovarian cancers into their constituent cells while preserving, as much as possible, their behavior within the tumor mass before resection. This award has allowed us to team up with collaborators in Germany to optimize sample preparation from the operating room to the bench (all samples, taken at diagnosis, are in a single-cell suspension within 4 hours post-resection). Thus, with such high-quality samples, we proceed to study their biology by a mass cytometry platform with two to four panels of 40 validated antibodies applied to each primary sample.

Although ovarian tumors are considered to be heterogeneous populations of cells, our preliminary analysis indicates that these tumors have a “structure” with finite boundaries, but tumors from individual patients inhabit those boundaries in different ways. Yet, pretty much everyone gets the same chemotherapeutic treatment regimen! The increased number of parameters measured at the single-cell level for each tumor allows us to live-sort potentially more disease-relevant cells



Drs. Zahnow (left) and Chiappinelli (right).



compared to previous studies. The overall goal of our work is to functionally characterize high-grade serous ovarian cancer cell subsets (through genetics, transcriptomics, and epigenetics) and relate that to clinical outcome. This will allow us to determine which are drug-resistant and why that is happening, building on associated cellular functional states and the hierarchy of cell types we have already mapped to the clinical and biological features in patients. We anticipate identifying new targets that will decrease drug resistance and potentiate cell killing of individual tumors. Drugs may already exist for these targets; if not, our research should provide a strong rationale for a new drug development program.

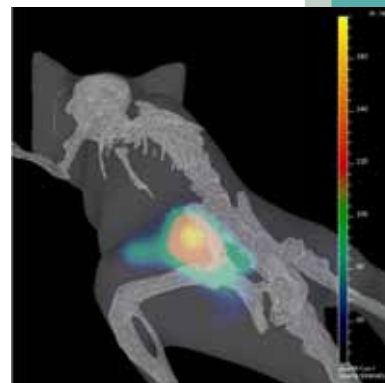
Update from FY12 Teal Innovator Paula T. Hammond, Ph.D., Massachusetts Institute of Technology, Koch Institute of Integrative Cancer Research

New approaches to combination therapy use the strategy of staged release of two or more therapeutics from a singular targeted nanoparticle. This can be accomplished by building a nanoparticle layer-by-layer, starting with a core that contains a chemotherapy drug relevant to ovarian cancer, such as cisplatin; then a second therapeutic can be introduced in the outer layers of the particle, such as an inhibitor that can lower or impede the function of tumor cells, or small interfering RNA (siRNA) molecules that can turn off a survival gene used by resistant tumor cell types to avoid attack by chemotherapy treatment. We have been partnering with clinicians and scientists at Dana-Farber Cancer Institute and at the Massachusetts General Hospital to determine and implement combinations key to ovarian cancer in these unique nanoparticle platforms. Ovarian cancers, particularly those of the high-grade serous subtype (96%), are characterized by mutations in the gene encoding the tumor suppressor protein, p53. In a recent collaboration with Dr. Michael Yaffe, also at the Koch Institute, we identified a novel downstream signal effector in the p38 MAPK stress response pathway – activated in response to platinum chemotherapy – whose loss is synthetic lethal in ovarian cancer cells that lack functional p53. To exploit this new vulnerability, we have engineered a series of lipid-like peptide co-polymers that self-assemble into nanoscale drug carriers that efficiently package and deliver siRNA and platinum chemotherapeutics specifically to ovarian cancer cells. Small interfering RNA delivered to cells with functional p53 is non-toxic, while potent cell killing is observed in ovarian tumor cells treated with platinum therapy. These nanotechnologies not only protect the siRNA from degradation during circulation, but they also improve the fraction delivered to the tumor, augmenting potential treatment response and minimizing dose-limiting toxic effects.

Our lab has been significantly impacted by the FY12 OCRP Teal Innovator Award. It has allowed us to build a meaningful team of graduate students and postdoctoral associates, including classically trained biologists and biomedical and chemical engineers who are dedicated to developing this technology to address the challenges of ovarian cancer. I spent a significant portion of my sabbatical last year visiting the Dana-Farber Cancer Institute, where I was able to learn a great deal more about the cancer cell biology of ovarian cancer, meaningful drug targets that can benefit from our nanoparticle approach, and the clinical needs for treatment of advanced stage cancer. These relationships have led to several new collaborations and interactions with my research team and clinical research teams who work closely with patients and can provide meaningful animal models, patient cancer cells, and expertise in the design of new therapies. An important aspect of our work is the ability to bring engineering expertise to the challenges of cancer by engaging with top biologists, oncologists, and other medical experts to understand the problem of recurrent forms of ovarian cancer and find ways to shut it down.



From left to right:
Postdoctoral Associates
Dr. Young Hoon Roh,
Dr. Kevin Shopsowitz, Dr. Erik
Dreaden, PI Dr. Paula
Hammond, Graduate
Student Santiago Echavarria,
Postdoctoral Associate
Dr. Lawrence Mensah,
Graduate Student Connie Wu,
and Postdoctoral Associate
Dr. Li Gu



Fluorescent siRNA (control sequence) delivered to a subcutaneous OVCAR3 tumor 24 hours post intraperitoneal injection in a mouse. The fluorescence indicates that the siRNA is localizing to the ovarian cancer tumor.

The Ovarian Cancer Academy in 2014

An Interactive Virtual Mentoring and Networking Platform

The Ovarian Cancer Academy, a virtual career development and research training platform, was created in FY09 to provide intensive mentoring, national networking, and peer group collaborative opportunities for junior faculty in ovarian cancer research. As expressed by FY09 OCRP IP member Dr. Michael Seiden, the OCRP chose to create the Academy because “the amount of science that needs to be covered to really get a global understanding of ovarian cancer is massive.... [I]t brings ... special opportunities for researchers because there’s a lot of room to make a difference, but it also requires... the ovarian cancer community to work hard to recruit young scientists, young clinical researchers into the field because we need more individuals to commit their time, energy, and talent to the problem.”

The Academy functions as an interactive entity across institutional boundaries to pair early career investigators (ECIs) with established mentors to foster successful, highly productive ovarian cancer investigators. The Academy Dean supports this process by facilitating regular communication among all Academy members and acts as an additional mentor to assess the research and career progress of the ECIs. The Academy is bearing fruit as its members take strides toward career sustainability in the field of ovarian cancer research, with promotions, tenure, publications, presentations, and additional grants received since the Academy’s inception. The OCRP is proud to expand the network of researchers dedicated to ovarian cancer research and looks forward to the wealth of knowledge and impact that these scientists are bringing to the field.

The Academy originated in FY09 with seven ECIs:



Martina Bazzaro, Ph.D., University of Minnesota; mentored by Amy Skubitz, Ph.D.

- Targeting ubiquitin-mediated protein degradation pathways for ovarian cancer treatment. Her research is focused on diagnostic and prognostic markers, targeted therapy, and the inhibitors’ potential mechanisms of anti-cancer activity.



Jeremy Chien, Ph.D., University of Kansas; mentored by Andrew Godwin, Ph.D.

- Investigating integrative functional genomics and proteomics to uncover mechanisms of chemotherapy resistance in ovarian cancer.



Panagiotis Konstaninopoulos, M.D., Ph.D., Dana-Farber Cancer Institute; mentored by Alan D’Andrea, M.D.

- Developing a biomarker for “BRCAness,” a phenotype characterized by responsiveness to platinum and PARP (poly ADP ribose polymerase) inhibitors and improved survival in patients.



Academy Dean Patricia Donahoe, M.D. Massachusetts General Hospital



Charles Landen, M.D., University of Alabama at Birmingham; mentored by Ronald Alvarez, M.D.

- Looking at the emerging aspect of cancer stem cells (i.e., tumor-initiating cells). His research is supportive of the hypothesis that subpopulations within heterogeneous ovarian tumors contribute to chemoresistance.



Kathryn Terry, Sc.D., Brigham and Women's Hospital; mentored by Daniel Cramer, M.D., Sc.D.

- Focused on understanding risk factors by etiologic pathway. Results from her work provide a better understanding of ovarian cancer risk factors, which is important for prevention.



Anda Vlad, M.D., Ph.D. Magee-Womens Hospital; mentored by Robert Edwards, M.D.

- Working on preclinical modeling of ovarian cancer for vaccine development. Her research is focused on the well-defined tumor antigen, MUC1, as an oncoprotein/vaccine candidate because it is overexpressed in more than 80% of epithelial ovarian cancers.



Rugang Zhang, Ph.D., Wistar Institute; mentored by Dario Altieri, M.D.

- Exploring how loss of Wnt5a by the cell activates Wnt signaling to overcome senescence, a state of arrested cell growth, contributing to the development of epithelial ovarian cancer.

Two new members were added to the Academy in FY12:



Geeta Mehta, Ph.D., University of Michigan; mentored by Ronald Buckanovich, M.D., Ph.D.

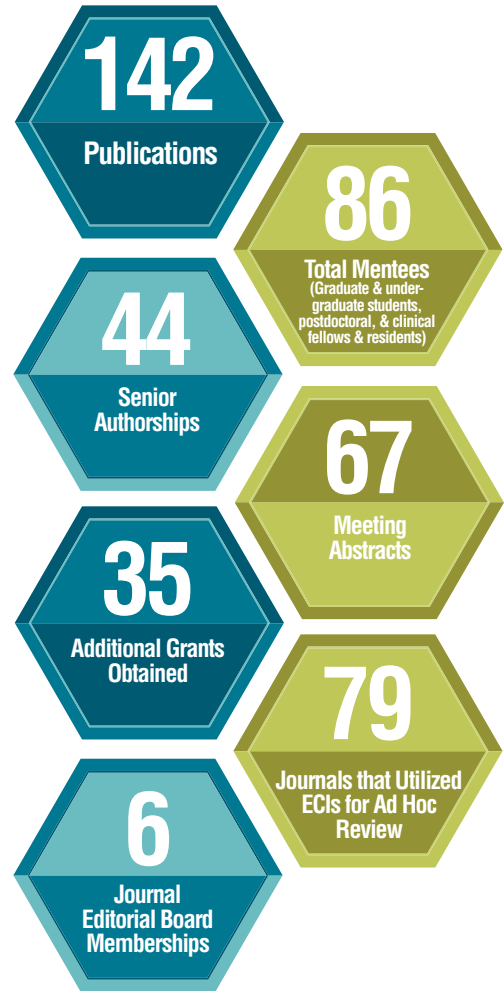
- Designing and developing a three-dimensional model to mimic the ovarian tumor microenvironment in vitro (outside of the patient).



Elizabeth Poole, Ph.D., Brigham and Women's Hospital; mentored by Shelley Tworoger, Ph.D.

- Examining psychosocial stress as a potential risk factor for ovarian cancer.

- The Academy is in the process of adding two additional members, recommended in FY13: Neil Johnson, Ph.D., from Fox Chase Cancer Center (mentored by Jeff Boyd, Ph.D.), who is examining the response of BRCA1 mutations to PARP inhibitors for better therapies and personalized medicine; and John Liao, M.D., Ph.D., from the University of Washington (mentored by Mary [Nora] Disis, M.D.), who is investigating the immune profiles of ovarian cancer for the development of a vaccine to prevent recurrent disease after primary treatment.



Risk and Prevention

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 are estimated to result in approximately 5%–10% of these cases. A recent study found that more than 40% of ovarian cancer patients with BRCA1/2 mutations had no reported family history of breast or ovarian cancers, suggesting that more women with ovarian cancer may have mutations in these risk genes than previously thought (*Journal of Clinical Oncology*, 2012). There are also environmental factors that may contribute to ovarian cancer risk. OCRP investigators are employing innovative approaches to understanding the risk factors of ovarian cancer and potential methods for prevention.



From right to left: Ming Lee, Sunday Stray, Elizabeth Swisher, Anne Thornton, Chris Pennil, Anneka Wickramanayake, Mary-Claire King, Siliva Casadei, Katy Pennington, and Tom Walsh.

Whole Genome Sequencing to Identify Novel Ovarian Cancer Genes

Tomas Walsh, Ph.D., University of Washington

For women who have inherited mutations in cancer predisposition genes such as BRCA1 or BRCA2, the risk of developing breast and/or ovarian cancer is greatly increased. Screening for these gene mutations has been a useful tool for preventing a subset of ovarian cancers, as mutation carriers can elect to have preventive surgery before the cancer arises. Even though women with known cancer predisposition gene mutations only account for a small subset of ovarian cancer cases, more individuals with ovarian cancer may have a strong family history of the disease in the absence of a known genetic mutation. Dr. Tomas Walsh of the University of Washington, recipient of an FY09 Idea Development Award, sought to identify additional ovarian cancer predisposing genes that may be present in these high-risk families. To do this, he used whole genome sequencing, looking at the sequence of the entire set of genes. Dr. Walsh identified five families with a strong history of breast and ovarian cancer that do not have any of the known cancer predisposition gene mutations, and he selected two members of each family with ovarian cancer for whole genome sequencing. Through this study, Dr. Walsh identified familial mutations in a gene called CHEK1, which coordinates the cellular DNA damage response and helps control cell division. He then screened large sets of other ovarian cancer samples and identified additional damaging CHEK1 mutations. These results suggest for the first time that CHEK1 may be a new ovarian cancer susceptibility gene. Further studies could lead to screening for CHEK1 mutations in high-risk families and may lead to the prevention of an additional subset of ovarian cancer.



Genetic Modifiers of Ovarian Cancer Risk in BRCA1 Mutation Carriers

Fergus Couch, Ph.D., Mayo Clinic and Foundation

Due to the heterogeneity of ovarian cancer onset, currently it is not possible to definitively identify BRCA1 mutation carriers who will go on to develop ovarian cancer in their lifetime, and those who will not. Dr. Fergus Couch was awarded an FY09 Idea Development Award to conduct a genome-wide association study to search for genetic modifiers that alter a BRCA1 carrier's susceptibility for developing ovarian cancer. Each so-called genetic modifier of risk probably confers only a small to moderate increase in the lifetime ovarian cancer risk. However, when several modifiers are inherited together, along with a BRCA1 mutation, the modifiers may have an important role in determining if and when a carrier develops ovarian cancer. Dr. Couch and the Consortium of Investigators of Modifiers of BRCA1/2 published their findings in 2013, linking two new genetic risk modifiers with increased risk of ovarian cancer. A change to the genetic code (single nucleotide polymorphism [SNP]) rs4691139 at the genetic location (locus) 4q32.3 appeared to be BRCA1-specific, with BRCA1 mutation carriers experiencing an approximately 20% increased risk over baseline when they had this additional mutation. A mutation in locus 17q21.31 at SNP rs17631303 increased the risk of ovarian cancer in BRCA1 mutation carriers by approximately 27% and was also significantly associated with ovarian cancer in BRCA2 mutation carriers and the general population. Based on these and other genetic modifiers of ovarian cancer risk in BRCA1 carriers, the 5% of BRCA1 mutation carriers at the lowest risk are predicted to have a 28% or lower lifetime risk of developing ovarian cancer, whereas the 5% at the highest risk will have a lifetime risk of 63% or higher. With improved risk assessment, women at the highest and lowest risk of ovarian cancer can be identified, and critical changes can be made to their clinical care.

Early Detection and Diagnosis

Previously believed to be the “silent killer,” most women with ovarian cancer do experience symptoms of the disease including bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, and urinary symptoms (urgency or frequency). Nevertheless, 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 of the disease, including the CA-125 blood test, transvaginal ultrasound, and pelvic exam. Investigators believe that it is possible to detect early ovarian cancer for all women. OCRP researchers are working toward the development of novel, minimally invasive tests for early detection and diagnosis.

Understanding the Role of the Immune System in the Outcome of Ovarian Cancer

Scott Abrams, Ph.D., Health Research Inc., Roswell Park Division, New York State Department of Health

While scientists and clinicians recognize that the immune system may be involved in cancer progression, there is still much to learn about how and when it is harmful and helpful for a given tumor. Dr. Scott Abrams was awarded a Pilot Award in FY10 to investigate the secretion of immune factors from ovarian cancers, and the role these chemical signals play in recruiting immune cells that suppress additional immune response. According to Dr. Abrams, he “hypothesized that a key target of such tumor-derived signals is the bone marrow, the birthplace of the immune army,” where it may promote a precursor of white blood cells, called myeloid cells. These specialized cells in turn prevent the rest of the immune system from attacking the tumor, as the cancer “takes hostage of the very institutions commissioned to provide host defense.” Dr. Abrams and his team implanted human ovarian cancer cell lines in a mouse model and identified six potential myelopoeitic factors (chemical signals for the myeloid cells). One of these, interleukin 6 (IL-6), was found to be significantly higher in ovarian cancer patients than in healthy controls, correlated with the accumulation of myeloid populations, and inversely associated with patient outcome (i.e., higher levels were associated with poorer outcomes). The level of IL-6 was measured primarily from ascites but also from sera taken from the mice. While the results are preliminary, these types of studies are needed to justify the use of resources to pursue potential biomarkers for disease detection and monitoring. Dr. Abrams hopes that the findings will also help “uncover novel treatment options that ambush the disease process in underappreciated or unconventional ways.”

A Targeted Approach to the Detection of Early-Stage Ovarian Cancer

Animesh Barua, Ph.D., Rush University Medical Center

Two of the earliest events in the development of ovarian tumors are changes in nuclear organization that result in the malignant transformation of cells and the generation of new blood vessels to support the growing tumor, called tumor-associated neo-angiogenesis (TAN). Dr. Animesh Barua hypothesized that a combination approach using serum markers for changes in nuclear organization [anti-NMP (nuclear matrix protein) antibodies] and TAN (IL-16, interleukin 16) with targeted ultrasound to vascular endothelial growth factor receptor-2 (VEGFR-2), an established marker of angiogenesis, will lead to improved diagnostic indices for the detection of early-stage ovarian cancer. He received an FY10 Translational Pilot Award to test this hypothesis in the laying hen model of spontaneous ovarian cancer. Dr. Barua demonstrated that ultrasound imaging with a VEGFR-2-targeted contrast agent improved the detection of ovarian tumors in hens compared to traditional ultrasound. Immunohistochemistry experiments confirmed that the frequency of microvessels expressing VEGFR-2 was higher in hens with ovarian tumors than in normal ovaries, supporting the increased signal intensity of the VEGFR-2-targeted agent in ovarian tumors. Using blood from hens, Dr. Barua provided evidence that both anti-NMP antibodies and IL-16 levels were increased with malignant transformation in the ovary and ovarian tumor development. Together, VEGFR-2-targeted ultrasound imaging with serum levels of anti-NMP antibodies and IL-16 enhanced the detection of ovarian tumors when it is limited to part of the ovary. Importantly, serum IL-16 levels were elevated prior to the development of a solid tumor mass in the ovary, suggesting that IL-16 could be a biomarker for early-stage ovarian cancer. This research represents an important step in the development of a novel approach for the diagnosis of early-stage ovarian cancer.



Understanding Ovarian Cancer and Recurrence

New discoveries continually help scientists, clinicians, and women learn more about the development and progression of ovarian cancer. As an estimated 70%–90% of women diagnosed with ovarian cancer go on to recur after initial treatment, understanding the mechanisms of recurrence is also an important area of study. OCRP researchers are taking unique approaches to gain a deeper understanding of ovarian cancer, which they hope will ultimately benefit women affected by the disease.

The Outcomes Consortium Development Awards: A Fresh Approach

Michael Birrer, M.D., Ph.D., Massachusetts General Hospital

Malcolm Pike, Ph.D., University of Southern California

Anil K. Sood, M.D., University of Texas MD Anderson Cancer Center



The overall survival of women with ovarian cancer has not changed appreciably over the last three decades. Despite this dismal reality, a minority of these patients become long-term survivors – defined as those who have survived at least 10 years from initial diagnosis. The Outcomes Consortium Development Award was created in FY12 to bring together teams of talented researchers focused on discovering what distinguishes the small subset of ovarian cancer patients who become long-term survivors. This award mechanism represents a new approach that seeks to characterize the biology and genomics of tumors belonging to long-term survivors, as well as identifying lifestyle factors that affect carcinogenesis and therapeutic response in these patients. The award is executed with a two-stage approach: an initial Development Award that enables the consortium to lay the groundwork for the research project, including proof of concept, and a second award that will support the full execution of the project. The knowledge gained through this largely unexplored area has the potential to yield insights that will lead to increased survival.

Each of the three consortia that received an FY12 Outcomes Consortium Development Award has a top-notch research team seeking to integrate biological and genomic signatures of ovarian cancers with information on treatment outcomes and lifestyle. Dr. Michael Birrer and his research team at the Massachusetts General Hospital plan to utilize the Gynecologic Oncology Group database to discover what separates long-term survivors of ovarian cancer from other patients. Genomic features (such as microRNA [miRNA] and methylation patterns) will be compared between long- and short-term survivors, as will immune responses. Dr. Malcolm Pike at the University of Southern California and his consortium will focus on the 20 percent of women diagnosed with high-grade serous ovarian cancer that survive past 10 years. The goal is to uncover the characteristics that contribute to long-term survival with a combined analysis of the tumors, treatments, and the patients themselves. Dr. Anil K. Sood at the University of Texas MD Anderson Cancer Center has assembled a consortium that seeks to understand long-term predictors in women with serous ovarian cancer. Using data collected over the past 15 years, the researchers will assess the power of biobehavioral and sociodemographic characteristics to predict long-term survival. They will also identify treatments and side effects that correlate with long-term survival.

By focusing on long-term survivors of ovarian cancer, we can hope that the OCRP Outcomes Consortium Development Award will give rise to new insights that will benefit ovarian cancer patients being treated today and help more become survivors tomorrow.

Predictors of Survival: Chemotherapy in Ovarian Cancer

Dong Liang, Ph.D., Texas Southern University

Platinum-based chemotherapy is a frontline treatment for ovarian cancer, although many women treated with these drugs have a recurrence that is resistant to these therapies. Dr. Dong Liang was awarded an FY06 Historically Black Colleges and Universities/Minority Institutions Collaborative Research Award to study the linkage between personal genetic markers and an individual's response to platinum-based therapies with the hope of providing improved and personalized cancer treatments. To better understand the mechanisms of personal genetics in response to treatment, Dr. Liang developed a DNA microarray to scan over 1,800 SNPs in 200 genes from 8 cellular and metabolic pathways believed to be associated with platinum chemoresistance, and he used the microarray to scan the DNA from the blood of ovarian cancer patients. These genetic data, along with clinical and demographic data, were used to determine personal genetic patterns linked to chemoresistance and overall survival. Individual analysis of the SNPs from these pathways yielded very interesting results, enabling Dr. Liang to categorize genotypes into low-, medium- and high-risk groups. In the miRNA pathway, he found 24 SNPs whose genotypes provided an 8.5-fold increase in overall survival time after chemotherapy when comparing low- and high-risk groups. Analysis of the mTOR (Mammalian Target of Rapamycin) signaling pathway showed 13 SNPs significantly associated with overall survival time after treatment; individuals who carried 8 or more of the unfavorable genotypes had decreased survival. In the telomere maintenance pathway, Dr. Liang found seven SNPs associated with survival; patients who carried five or more of the unfavorable genotypes had a fourfold reduced overall survival rate over low-risk groups who carried two or less of the unfavorable genotypes. In total, Dr. Liang identified 111 SNPs that were significantly associated with overall survival after platinum-based treatments. He hopes to use this information to predict clinical outcomes of ovarian cancer patients and provide better cancer care.

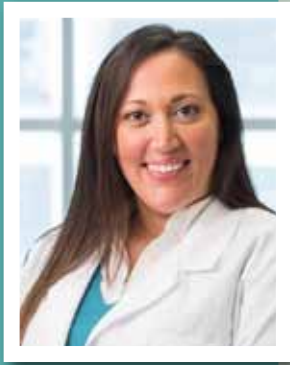
Identifying Mechanisms of Chemoresistance in Ovarian Cancer

Jin Cheng, M.D., Ph.D., H. Lee Moffitt Cancer Center and Research Institute

In FY07, Dr. Jin Cheng received a Concept Award to identify miRNAs (small RNA sequences that negatively regulate gene expression) involved in ovarian cancer chemoresistance. He detected the co-upregulation of miRNAs miR-221/222, miR-214, and miR-200a in cells that are resistant to cisplatin, a chemotherapy drug that is used to treat several types of cancers, including ovarian cancer. With funding from an FY10 Translational Pilot Award, Dr. Cheng built upon his previous findings and continued his work with miRNAs.

Dr. Cheng identified and characterized an inhibitor of miR-214, MCCRI. His initial cell culture studies showed that MCCRI not only binds directly to miR-214, but also inhibits the survival of cells that express high levels of miR-214. Additional cell culture studies showed that miR-214 promotes the migration and invasion of ovarian cells, but this was largely inhibited by MCCRI. Animal studies also showed that tumor growth was significantly reduced in mice that were injected with miR-214-high cells and subsequently treated with MCCRI. Finally, he was able to demonstrate that MCCRI inhibits ovarian cancer stem cells, and also, more significantly, that MCCRI synergizes with the chemotherapy drug cisplatin and inhibits the growth of cells that are cisplatin-resistant. Therefore, MCCRI could show promise as a therapeutic agent for ovarian cancer, especially in cases of cisplatin resistance.





Photographer David Schwartz , Case Western Reserve University (CWRU), and the photograph is being used courtesy of CWRU.

Characterization of miRNA Signatures Associated with Epithelial Ovarian Cancer Chemoresistance

Analisa DiFeo, Ph.D., Case Western Reserve University

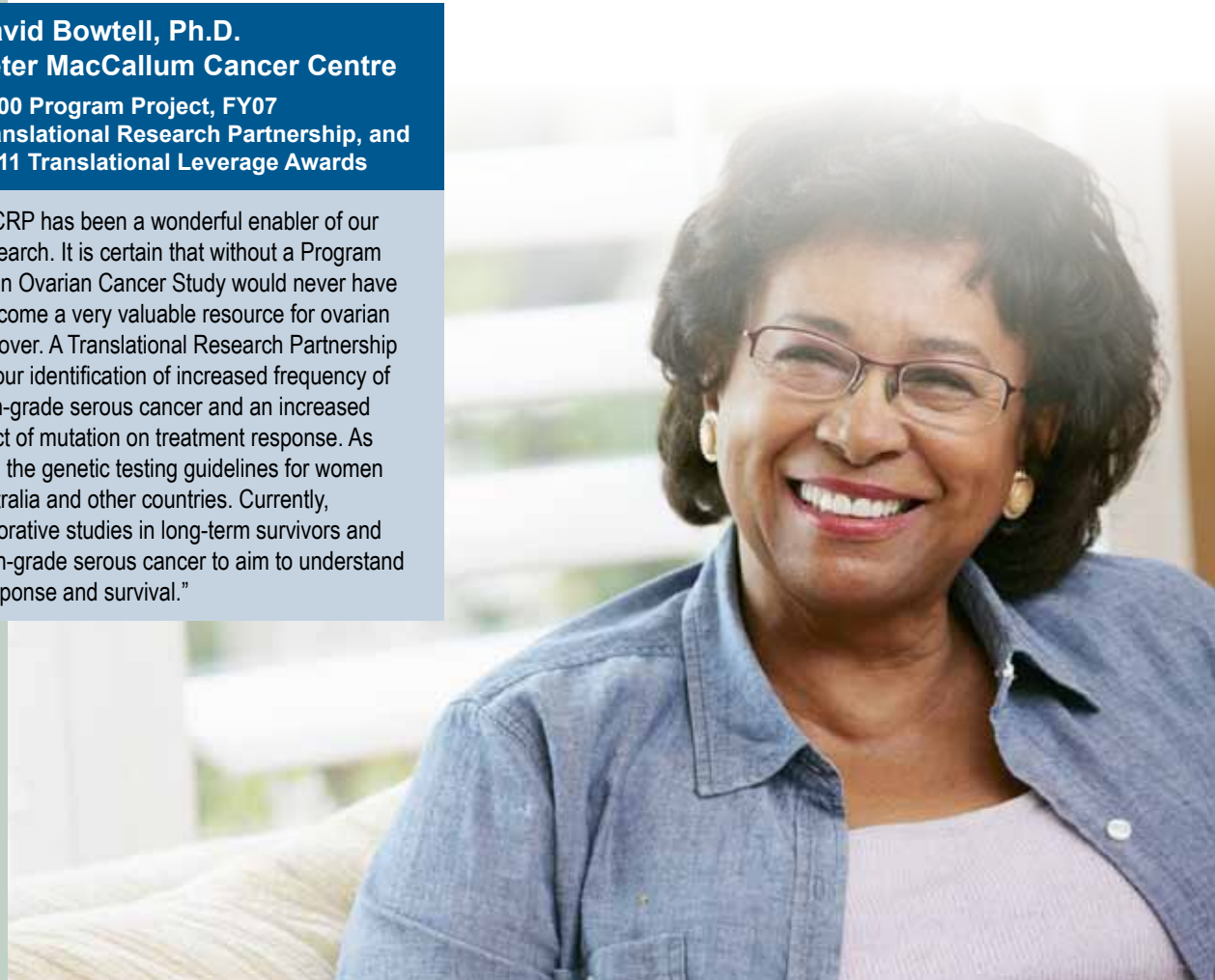
Epithelial ovarian cancer (EOC) represents about 90% of ovarian cancer cases and has the highest mortality rate among gynecological malignancies. A majority of women with EOC who initially respond to therapy go on to recur, mainly due to the development of resistance to current chemotherapeutic drugs. Dr. Analisa DiFeo, with support from an FY10 OCRP Translational Pilot Award, sought to determine markers of EOC recurrence and chemoresistance in order to develop better diagnostics and possible therapies for these women. To do this, she assessed changes in miRNA levels, which are small non-coding RNA molecules that negatively regulate gene expression. She found that a particular miRNA, miR-181a, was highly expressed in high-grade, chemoresistant EOC and that overall survival was significantly lower for patients with high miR-181a expression. Through cell and animal experiments, Dr. DiFeo found that miR-181a expression increased cell survival, chemoresistance, motility, and invasion, and led to a dramatic increase in tumor metastases in mice. Furthermore, expression of miR-181a caused ovarian cancer cells to undergo epithelial-mesenchymal transition (EMT), a cellular process by which cells lose polarity and cell-cell adhesion properties, and become migratory and invasive. She further elucidated the precise mechanism of miR-181a-induced EMT and determined that it directly inhibits the Smad7 gene, which normally suppresses the TGF β gene signaling pathway, a potent inducer of metastasis. These findings suggest that miR-181a could be a prognostic biomarker to identify which women are at a high risk of recurrence and which will respond to current therapies. Moreover, miRNA inhibitors are currently in development for the treatment of many types of cancer; thus, miR-181a may serve as an important therapeutic target for recurrent, chemoresistant ovarian cancer.



David Bowtell, Ph.D.
Peter MacCallum Cancer Centre

**FY00 Program Project, FY07
Translational Research Partnership, and
FY11 Translational Leverage Awards**

“OCRP has been a wonderful enabler of our research. It is certain that without a Program grant in 2001, the Australian Ovarian Cancer Study would never have gotten off the ground to become a very valuable resource for ovarian cancer research the world over. A Translational Research Partnership Award in 2007 resulted in our identification of increased frequency of BRCA1/2 mutations in high-grade serous cancer and an increased understanding of the impact of mutation on treatment response. As a result, this work changed the genetic testing guidelines for women with ovarian cancer in Australia and other countries. Currently, OCRP is supporting collaborative studies in long-term survivors and molecular subtyping of high-grade serous cancer to aim to understand determinants of patient response and survival.”



Treatment and Recurrence

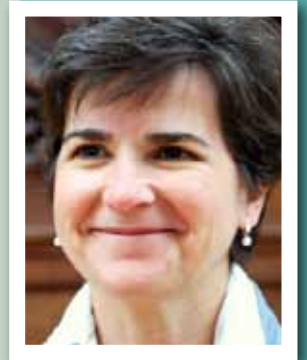
While most ovarian cancers respond to initial chemotherapy and/or radiation treatments, only 44% of women diagnosed with ovarian cancer reach 5 years of survival post-diagnosis (American Cancer Society, 2014). OCRP investigators are conducting groundbreaking research into treatments for primary and recurrent diseases.

Uncovering Novel Therapeutic Targets in Ovarian Cancer Using Mesenchymal Stem Cells (MSCs)

Aline Betancourt, Ph.D., Tulane University

Safe and effective therapies to treat ovarian cancer continue to be needed, as the efficacy of existing treatments is limited in a large number of patients. One potential cell-based therapy uses MSCs; they are easily obtained from adult tissues (either from the patient or an outside donor), expandable in number, easily stored outside the body without significant impact to their capabilities, and naturally self-locate to sites of inflammation and cancer. However, a concern is that while MSCs can home to tumors, they have been shown to sometimes support tumor growth and metastasis. Therefore, studies are needed in order to understand the role of MSCs in ovarian tumor growth and metastasis.

Dr. Aline Betancourt was awarded an FY07 Concept Award to explore the chemical signaling that brings MSCs to the tissues immediately surrounding an ovarian cancer tumor (its microenvironment), as manipulation of the microenvironment may change it from one that promotes tumor growth to one that suppresses and attacks the tumor. These studies confirmed the recruitment of MSCs to the tumor microenvironment, and that they played a role in tumor promotion. However, pre-treating MSCs with certain types of molecules and proteins reduced this effect. Dr. Betancourt was then awarded a Teal Expansion Award in FY11 to understand the tumor suppressive subtype of MSCs (MSC1) and explore MSCs as a potential therapeutic for ovarian cancer. She has developed a standardized method of treating MSCs to obtain MSC1s, for which she has filed a provisional patent. In published studies, these MSC1s have reduced the volume of ascites and led to changes in the tumor microenvironment that suppressed tumor cells. More recent studies showed that MSC1s kill tumors by direct secretion of a molecule called TRAIL, which only targets cancer cells. Furthermore, the studies demonstrated that MSC1s can reawaken the anti-tumor immunity shut off by the tumors. Thus, MSC1 therapy may be considered to be a new kind of cancer immunotherapy. Not only does the MSC1 therapy directly kill the tumor with TRAIL, but it can also turn the host immune cells back on to reject the tumor cells. Cancer immunotherapies are showing remarkable success in the clinic, with some cancer patients developing cures to their disease. These are very promising observations that Dr. Betancourt is simultaneously preparing for potential early phase trials in humans. Dr. Betancourt's OCRP funding has allowed her to make new discoveries and refine a potential low-toxicity and effective therapy for ovarian cancer.



Amit Oza, M.D.

University Health Network, Toronto

FY11 Translational Leverage, FY12 Synergistic Translational Leverage, and FY13 Clinical Translational Leverage Awards

“Support for high-return projects through the Ovarian Cancer Research Program is allowing our program to strategically partner with scientists in the lab. Together, we have created a niche environment where soon, findings from the lab can be taken directly to the clinic and back into the lab for further investigation. These funds are allowing our team to devise and develop innovative research projects that may lead to 1) new approaches as to how physicians select new anti-cancer drugs for clinical investigation; 2) drugs that are able to hone in and target tumor tissue with particles that are invisible to the naked eye; and 3) helping physicians determine, in real time, how a patient is responding to targeted therapy, and if their treatment course should be changed. Without OCRP support, these innovative and high-return projects wouldn't be possible.”



Inhibition of Small GTPases as a Novel Therapeutic Approach in Ovarian Cancer

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

Small GTPases, including Rab, Ras, and Rho family members, are involved in protein trafficking (movement within a cell), cell proliferation, and cell migration. This makes them attractive therapeutic targets for ovarian cancer treatment. With support from an FY07 Concept Award, Dr. Laurie Hudson and Dr. Angela Wandinger-Ness of the University of New Mexico (UNM), collaborated with Dr. Larry Sklar to conduct a high-throughput molecular screen to identify inhibitors of small

Left to right: Carolyn Muller, M.D., Laurie Hudson, Ph.D., and Angela Wandinger-Ness, Ph.D.

GTPases Rac1 and Cdc42, which are often upregulated in ovarian cancer. Through this screen, they identified an enantiomer (chemical orientation) of the U.S. Food and Drug Administration (FDA)-approved nonsteroidal anti-inflammatory drug (NSAID) naproxen as a potential inhibitor against ovarian cancer cell metastasis. Cheminformatic analysis conducted by Dr. Tudor Oprea of UNM predicted an enantiomer of the FDA-approved NSAID ketorolac (Toradol) as an additional Rac1 and Cdc42 inhibitor. With funding from an FY11 Teal Expansion Award, Dr. Hudson, Dr. Wandinger-Ness, and clinical collaborator Dr. Carolyn Muller, identified that the compound was effective at inhibiting Rac1 and Cdc42 activity and reducing tumor burden in ovarian cancer cell lines, mouse models, and patient-derived cells. The investigators have begun testing ketorolac in ovarian cancer in patients and found that the compound distributes effectively to the peritoneal compartment and is safe to use in this patient population. Furthermore, initial analysis of patient samples has shown that ketorolac decreases Cdc42 and Rac1 activity, and reduces tumor cell adhesion to fibronectin or collagen, hallmarks of cancer cell metastasis. These initial results are promising, and additional studies are ongoing with the hopes of expanding the clinical trials evaluating ketorolac use in ovarian cancer patients.



Preclinical Testing to Improve the Efficacy of Chemotherapy in Ovarian Cancer

Andre Lieber, M.D., Ph.D., University of Washington

The majority of ovarian cancers develop from the epithelium (surface cells) of the ovary. Epithelial cells possess intercellular junctions that allow the cells to bind tightly together; this can impede delivery of chemotherapies to cells within the tumor. The ability to loosen these bonds would give chemotherapies greater access to the internal structure of the tumor. Dr. Andre Lieber received an FY11 Translational Pilot Award to gather preclinical information on JO-1 (junctional opener-1), a drug with the potential to open these junctions, with the goal of moving forward to a clinical trial. If clinically viable, a drug breaking intercellular junctions could allow for the administration of less toxic doses of chemotherapy.

In the first year of this award, Dr. Lieber found that JO-1 was well tolerated in a transgenic mouse model. The drug also allowed for pre-existing anti-tumor T cells produced by the immune system to enter the tumor. Administered alone, the drug caused complete tumor regression in 60% of mice. When JO-1 was used in conjunction with the chemotherapy agent Doxil, the amount of Doxil found within the tumor increased 10-fold and was found deeper within the tumor than when administered as a single agent. Dr. Lieber continues to test combinations of chemotherapies and JO-1 to determine the best approach for the use of the drug. Through this award, Dr. Lieber has gathered additional data needed to apply for investigational new drug approval from the FDA in preparation for a clinical trial.



**Brad Nelson, Ph.D.
British Columbia Cancer Agency**

**FY00 New Investigator, FY08 Idea Development, and
FY11 Teal Expansion Awards**

"I'm thankful to the OCRP for taking a chance on an outside-the-box idea my colleagues and I came up with. It's well established that the immune system responds to ovarian cancer, and this is associated with increased patient survival. But we didn't know what was triggering these responses. A few years ago, we had a hunch that the immune system might be recognizing mutations in the patient's tumor. With funding from OCRP, we recently showed that this does indeed happen. Based on this discovery, we're now designing a clinical trial in which patients will be given mutation-specific T cells that can recognize and destroy their tumors."

Game-Changing Research



Significantly Impacting the Standard of Care and/or Challenging Current Paradigms in Ovarian Cancer

Animal Models

*Dr. Denise Connolly: **Mouse model of ovarian leiomyosarcomas***

*Dr. Louis Dubeau: **Mouse model with homozygous BRCA1 knockout restricted to ovarian granulosa cells***

*Dr. Tyler Jacks: **Mouse model of ovarian cancer associated with endometriosis***

*Dr. Sandra Orsulic, Dr. Deyin Xing: **Mouse model for BRCA1-associated ovarian carcinoma***

*Dr. Gus Rodriguez, Dr. Patricia Johnson, Dr. Dale Hales, Dr. Judith Luborsky: **Chicken models of ovarian cancer***

*Dr. Rong Wu: **Mouse model of human ovarian endometrioid cancer***

Biomarkers

*Dr. George Coukos: **Panel of 13 promising genes as ovarian cancer biomarkers***

*Dr. Patricia Kruk: **Bcl-2 as a urinary biomarker for ovarian cancer***

*Dr. Martin McIntosh: **MMP7 elevated in serum up to 3 years prior to diagnosis of ovarian cancer***

*Dr. Samuel Mok: **New biomarkers for early-stage ovarian cancer: osteopontin, protease M, and lysophosphatidic acid***

*Dr. Tian-Li Wang, Dr. Ie-Ming Sheh: **Rsf-1 as a prognostic indicator***

Decision-Making Resources

*Dr. David Bowtell: **Discovered that the Asn372His genotype of BRCA2 significantly increases the risk of ovarian cancer, which is now used to assess a woman's risk for developing ovarian cancer when undergoing BRCA screening.***

*Dr. Fergus Couch: **Identified a genetic locus associated with risk of ovarian cancer in BRCA1 mutation carriers, but not in BRCA2 mutation carriers or the general population.***

*Dr. Mary Daly: **Ovarian Cancer Risk-Reducing Surgery: A Decision Making Resource (a book available at no cost to the public).***

*Dr. Tomas Walsh: **Confirmed loss-of-function mutation in RAD51D gene predisposes women without BRCA1/2 mutations to ovarian cancer but not breast cancer. This information has helped guide genetic testing kits for women in families with ovarian cancer with or without breast cancer.***

*Dr. Zhen Zhang: **OVA1™*, the first in vitro diagnostic multivariate index assay of proteomic biomarkers cleared by the U.S. Food & Drug Administration to help physicians determine if a pelvic mass is benign or malignant before it is removed.***

* OVA1, an in vitro diagnostic multivariate index test, is approved by the FDA and is the only approved blood test to help determine if an ovarian mass is malignant or benign prior to surgery, facilitating surgical planning and identifying patients for referral to a gynecologic oncologist.

Therapies

Dr. Jin Q. Cheng: Inhibitors of AKT/PKB with anti-tumor activity in ovarian cancer.

Dr. Stephen Howell: Showed that human Copper Transporter 1 (hCTR1) was necessary to transport platinum-based drugs into cells; resistance could be conferred by the cell degrading hCTR1. Multiple clinical trials are now treating with a proteasome inhibitor in conjunction with platinum-based therapy to boost efficacy.

Dr. Panagiotis Konstantinopoulos: Developed a gene expression profile that can identify tumors with the BRCAness phenotype and demonstrated that these BRCA-like tumors are more sensitive to platinum and PARP inhibitors.

Dr. Gillian Mitchell, Dr. David Bowtell: Identified that 44% of women with non-mucinous ovarian cancer and mutations in BRCA1/2 did not have a family history; also identified that women with BRCA1/2 mutations had improved responses to platinum-based chemotherapy at frontline and relapse treatments. As a direct result, the genetic testing guidelines in Australia were changed to include all women under the age of 70 diagnosed with non-mucinous ovarian cancer.

Dr. Nouri Neamati: Developed substituted pyrimidyl guanidine derivatives having anticancer activity, particularly in ovarian cancer.

Dr. Xiaoliu Zhang: Developed the oncolytic virus FusOn-H2 to induce a patient's immune system to attack tumors.

Tissues and Associated Clinical Data

Dr. David Bowtell: Australian Ovarian Cancer Study (AOCS) – Multicenter, population-based resource involving collection of linked epidemiologic and clinical data and biospecimens from 2,500 women presenting with potential ovarian cancer, resulting in 1,859 cases (1,719 questionnaires, 1,694 blood samples, and 1,100 frozen tissue samples) and 1,073 matched controls (1,072 questionnaires and 924 blood samples) to study ovarian cancer risk factors and biomarkers. Followup continues on about 1,000 women.

Dr. Georgia Chenevix-Trench: 1,839 ovarian epithelial and the fibroblast cell samples (675 ovarian cancer cases and 1,164 controls).

Dr. Beth Karlan: Human ovarian tissue and clinical database containing ovarian carcinomas (152) and benign ovaries (110).

Dr. Santo Nicosia: Ovarian cancer tissue repository with more than 600 samples.

Dr. Patricia Shaw: Toronto Ovarian Cancer Research Network – A repository of prophylactic surgery specimens from BRCA mutation carriers with a database of BRCA mutation carrier and control group gene expression signatures.

Dr. Nicole Urban: Repository with over 6,000 individually identified ovarian tissue specimens.

Innovative Collaborations

Dr. Andrew Berchuck: International Ovarian Cancer Association Consortium (OCAC) – The group includes over 50 case-control studies and is working together to identify ovarian cancer susceptibility polymorphisms and lifestyle risks for ovarian cancer.

Dr. Igor Jurisica: OPHID/I2D – Online databases of known and predicted protein–protein interactions (PPIs). NAViGaTOR – Software package for visualizing and analyzing PPI networks.

Dr. Robert Kurman: Inclusive scoring algorithm that incorporates morphologic and immunohistochemical results. Website for this algorithm should be able to help pathologists diagnose serous tubal intraepithelial carcinomas (STICs).

In the Pipeline

Exceptionally promising early results in ovarian cancer research

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

Founded the International Ovarian Cancer Association Consortium, which has published findings regarding genetic and lifestyle risks for ovarian cancer, including that tubal ligation significantly reduced risk for invasive endometrioid and clear cell ovarian cancer, with lesser reduction in risk seen for invasive serous and mucinous ovarian cancers; that low-dose regular aspirin use significantly reduced ovarian cancer risk; and that use of genital powder is not associated with ovarian cancer.

Dr. Panagiotis Konstantinopoulos – Gene Expression Profile

Developed the BRCAness gene expression profile, which can identify tumors with the “BRCAness” phenotype (characterized by increased sensitivity to platinum analogues and PARP inhibitors as well as improved survival), and has identified inhibition of HSP90 may improve sensitivity of these tumors to PARP inhibitors.

Dr. James Cooper – Innovative T Cell-Targeted Therapy

Developing universal T cells for immunotherapy that does not require the patient to donate cells for their own therapy; in mouse models, these effectively eliminated implanted human-derived ovarian cancer cells. Concurrently, he is confirming receptor tyrosine kinase-like orphan receptor-1 (ROR1) as an ovarian cancer-specific target for these cells.

Dr. David Bowtell – BRCA Mutations and Ovarian Cancer Subtypes

Identified that BRCA1 mutant tumors are associated with a specific molecular subtype of high-grade serous carcinoma and have a distinct gene expression signature, which is heavily influenced by specific amplification events at 8q24 and on the X chromosome. By contrast, BRCA2 mutant tumors more closely resemble “wild-type” high-grade serous carcinoma.

Drs. Elizabeth Swisher and Anton Krumm – Elucidating Ovarian Carcinogenesis

Identified a premalignant expression signature that may reflect early steps in BRCA1-mediated ovarian carcinogenesis.

Dr. Nouri Neamati – Testing Potential New Therapies

Preclinical tests on a small-molecule gp130 inhibitor (SC144) indicate it is able to delay tumor growth without affecting normal tissue when administered orally in a mouse model.

Dr. Sally Kornbluth – Identifying New Avenues for Therapy

Identified that inhibition of fatty acid synthase by drugs such as orlistat induced ovarian cancer cell death through a series of signals in the cell that result in induction of caspase 2, leading to apoptosis (programmed cell death).

Dr. Eleanor Rogan – Non-invasive Detection for Risk and Prevention

Identified significantly higher levels of DNA-estrogen adducts in urine samples of women with ovarian cancer compared to controls, indicative of unbalanced estrogen metabolism.

Dr. Rugang Zhang – Prognostic Indicator and Therapeutic Target for Epithelial Ovarian Cancer

Determined that Wnt5a, a noncanonical Wnt ligand, induces cellular senescence by activating histone repressor A/ promyelocytic leukemia senescence pathway. Wnt5a suppresses the growth of EOC, and loss of Wnt5a predicts a poor outcome in EOC patients.



Looking to the Future

A sampling of research awards recommended for funding in FY13 (in addition to the Teal Innovator and Ovarian Cancer Academy–Early Career Investigator award mechanisms)

Pilot Award

Supports conceptually innovative, high-risk/high-reward research that could ultimately lead to critical discoveries or major advancements that will drive the field of ovarian cancer forward.

Dr. Elizabeth Swisher

Evaluating whether the Fanconi anemia DNA repair pathway can predict benefit from the addition of bevacizumab to combination chemotherapy.

Dr. Jennifer Barton

Developing a miniature optical imaging device, called a falloposcope, to screen for ovarian cancer without general anesthesia or tissue incision.

Dr. Melissa Gellar

Developing a mobile phone application to educate ovarian cancer survivors on the benefits of genetic counseling.

Dr. Shuang Huang

Evaluating the combination of phosphodiesterases 1C and 2A inhibitors as a means to treat metastatic ovarian cancers in a well-established mouse model.

Dr. Richard Sloan

Evaluating whether an increased walking intervention will reduce chemotherapy-induced cognitive dysfunction (“chemo brain”).

Clinical Translational Leverage Award

Supports the leveraging of existing human-based ovarian cancer resources in translational research to address high-impact research ideas or unmet needs in ovarian cancer.

Dr. Kala Visvanathan

Investigating whether use of statins (cholesterol-lowering drugs) improves survival in women with epithelial ovarian cancer.

Dr. Sandra Orsulic

Linking genetic information with clinical outcome to develop an identifying signature for women who are likely to quickly relapse.

Resource Development Award

Supports product-driven research aimed at developing well-annotated tools for use by the ovarian cancer research community.

Dr. Tan Ince

Developing a novel cell culture approach to examine cellular differences (heterogeneity) within a single tumor and evaluate cellular responses to different treatments.

**For additional information
on awards recommended for funding:
<http://cdmrp.army.mil/search.aspx>**

Don't Miss Our...

**“Changing the Odds” video (<http://www.youtube.com/watch?v=f6TvfnmYOIA>)
and “OCRP Patient Advocates: Partnering Toward a Cure” video
(http://www.youtube.com/watch?v=Hm1Hf2sy9So&list=UUj6XwkUo_5LR-GA2PiaZCQ)**



For more information, visit

<http://cdmrp.army.mil>

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usarmy.detrick.medcom-cdmrp.mbx.cdmrp-public-affairs@mail.mil

(301) 619-7071

