

Ovarian Cancer Research Program

DEFENSE HEALTH PROGRAM

Impact of the DOD OCRP

The Ovarian Cancer Research Program has produced many high-impact advances in the prevention, detection, diagnosis, and treatment of ovarian cancer, including:

Prevention, Detection, and Diagnosis

- RAD51D Genetic Testing Kit
- OVA1™ Diagnostic Index Test
- Genetic Testing Guidelines for Ovarian Cancer
- A Computational Approach to Diagnosing Precursor Lesions to Ovarian Cancer
- Ovarian Cancer Risk-Reducing Surgery: A Decision Making Resource

Treatment

- Targeting Tumor Vasculature to Eliminate Ovarian Cancer Cells
- Using MSC1 Immunotherapy to Create an Anti-tumor Response
- Virus-based Toxin Delivery for Ovarian Cancer Tumors
- Using NSAIDs to Treat Ovarian Cancer

New Research Tools

- New Animal Model of Spontaneous Epithelial Ovarian Cancer
- New Model to Study the Effect of BRCA1 on Ovarian Cancer
- New Endometriosis Ovarian Cancer Animal Models
- The Effect of Two Oncogenes on the Development of Ovarian Leiomyosarcoma
- Using Animal Proteins to Predict Ovarian Cancer Risk in Humans
- The Ovarian Cancer Research Academy

VISION: Eliminate ovarian cancer

MISSION: To support patient-centered research to prevent, detect, treat, and cure ovarian cancer

Ovarian cancer is a devastating disease. It is responsible for more deaths than any other cancer of the female reproductive system. In 2015, just over 21,000 new cases of ovarian cancer were diagnosed, and over 14,000 women died of the disease – one of the highest ratios of mortality to incidence of any cancer.

The Department of Defense (DoD) Ovarian Cancer Research Program (OCRP) was established in 1997 to define and address the critical research gaps facing the ovarian cancer community. DoD OCRP is the leading funder of new ovarian cancer research projects and the second-leading funder overall of ovarian cancer research in the United States. With \$276 million in Congressional appropriations between FY97 and FY16, the DoD OCRP has funded 372 research awards, resulting in over 1,200 peer-reviewed publications, nearly 100 patent applications, and high-impact advances in the prevention, screening, diagnosis, and treatment of ovarian cancer. The DoD OCRP has transformed the landscape of ovarian cancer, to the benefit of patients everywhere.

The success of the DoD OCRP can be attributed to the synergistic efforts of many talented and dedicated individuals. A hallmark of the DoD OCRP is the partnership of ovarian cancer survivors and advocates with scientists and clinicians, all of whom work together to set program priorities, design funding opportunities, evaluate research applications, and identify high-impact, innovative research that will lead to the elimination of ovarian cancer. The disease survivors lend their unique perspectives on the human dimension of the disease, to support research that reflects their own concerns as well as those of the clinicians who treat them.

GAP 1

Understand how all types of ovarian cancer begin, grow, and metastasize

GAP 1 & GAP 2

New Models to Study the Effect of BRCA1 on Ovarian Cancer

Developed a new mouse model which deleted the BRCA1 gene from ovarian cells. This was found to result in cystic tumors forming in the ovaries and uterine horns. Another novel transgenic mouse strain provided a unique experimental model to study the sensitivity of ovarian tumors to various therapies that may interfere with the immune system. Together these models may help reveal the etiology of hereditary ovarian cancers, and help evaluate therapies that target the BRCA1 pathway.

Louis Dubeau University of Southern California; Sandra Orsulic, Cedars-Sinai Medical Center

GAP 1 & GAP 2

The Effect of Two Oncogenes on the Development of Ovarian Leiomyosarcoma

Generated a new mouse model that inactivated both BRCA1 and p53, two oncogenes that have individually been implicated in the development of epithelial ovarian cancer. Surprisingly, this work demonstrated that inactivating both genes at once actually reduces the chance of developing epithelial ovarian carcinomas, a new insight into genetic contribution to ovarian cancer development. This research also produced a novel tumor cell line for ovarian leiomyosarcoma.

Denise Connolly, Fox Chase Cancer Center

GAP 1 & GAP 2

New Endometriosis Ovarian Cancer Animal Models

Developed a new mouse model of ovarian cancer that more closely

GAP 2

Create new tools for studying ovarian cancer

resembles the morphological features, biological behavior, and gene expression profiles of human cancers. This model should help advance understanding of the pathogenesis of human ovarian cancer and will likely prove useful for preclinical testing of therapies. Two additional mouse models, for endometriosis and endometrioid ovarian adenocarcinoma, were developed and provide invaluable insight into the pathogenesis of ovarian cancer, testing molecular therapies, and developing methods of early detection and cancer prevention.

Rong Wu, University of Michigan; Tyler Jacks, Massachusetts Institute of Technology

GAP 2

New Animal Model of Spontaneous Epithelial Ovarian Cancer

Validated and supported the functional use of hens as a model of spontaneous ovarian cancer. This strain of hen develops epithelial ovarian cancer, similar to human disease. This work helped identify molecular targets for therapeutic intervention, and supported the use of the hen as a low-cost model for large-scale pre-clinical studies of targeted therapeutics.

Dale B. Hale, Southern Illinois University

GAP 2 & GAP 3

Using Animal Proteins to Predict Ovarian Cancer Risk in Humans

Developed a large bio-repository of reproductive tract cancers from hens of varying ages, strains, reproductive history, and chemopreventive drug exposure. This led to standardized histological criteria to describe ovarian tumors in the hen model. Genetic research determined p53

GAP 3

Increase prevention and improve quality of life for survivors

and HER2 are similar between humans and chicken ovarian cancer. Additional research using archived hen serum demonstrated that the protein AOA can act as a predictive marker for ovarian cancer development. This can aid in developing a screening test for early detection of ovarian cancer, as many proteins that are associated with human ovarian cancer, including AOA, are also found in hens with ovarian cancer.

Gustavo Rodriguez, NorthShore Research Institute; Judith Luborsky, Rush University Medical Center

GAP 3

Ovarian Cancer Risk-Reducing Surgery: A Decision Making Resource

Supported research contributing to the preparation of a book, *Ovarian Cancer Risk-Reducing Surgery: A Decision Making Resource*. This resource assists women who carry the BRCA1/2 gene or have a family history of ovarian cancer, in determining whether or not to undergo prophylactic oophorectomy as preventive measure. This resource is available at no cost online (http://www.igcs.org/files/TreatmentResources/OCRRS_2008.pdf). For a paper copy, email surgerybook@fcc.edu with your name, address, and reason for requesting the book.

Mary Daly, Fox Chase Cancer Center

GAP 3 & GAP 4

Genetic Testing Guidelines for Ovarian Cancer

Identified that 44% of women with non-mucinous ovarian cancer and mutations in BRCA1/2 did not have a family history. As a result, genetic testing guidelines in Australian

GAP 4

Devise and advance new and improved techniques to diagnose and treat ovarian cancer

Familial Cancer Clinics and other countries were changed to include all women diagnosed under the age of 70. Implementing these changes should save lives by identifying those at risk more effectively than current strategies, and also by improving current and experimental treatment regimes.

Gillian Mitchell and David Bowtell, Peter MacCullum Cancer Centre

GAP 3 & GAP 4

A Computational Approach to Diagnosing Precursor Lesions to Ovarian Cancer

Supported a multi-institutional, multi-approach award to investigate early changes that lead to ovarian high-grade serous cancer, a disease whose 5-year survival rate is only 27%. This research developed and validated an algorithm to help pathologists diagnose STIC (serous tubal intraepithelial carcinoma), which are precursor lesions to ovarian cancer. The algorithm is available online at: <http://www.ovariancancerprevention.org/>.

Robert Kurman, Johns Hopkins University

GAP 4

RAD51D Genetic Testing Kit

Loss-of-function mutation in the RAD51D gene predisposes women without BRCA1/2 mutations to ovarian cancer, but not breast cancer. This information helped guide genetic testing kits for women in families with ovarian cancer with or without breast cancer. This work is cited as part of the foundational logic leading to a commercially available genetic testing kit from Ambry Genetics.

Tomas Walsh, University of Washington

GAP 5

Investigate tumor response and/or resistance to treatment

GAP 4

OVA1™ Diagnostic Index Test

Discovered, identified, and validated five serum biomarkers for use in detecting ovarian cancer. 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.

Zhen Zhang, Johns Hopkins University

GAP 4

Using NSAIDs to Treat Ovarian Cancer

Repurposed the use of non-steroidal anti-inflammatory drugs (NSAIDs) to inhibit ovarian cancer cell adhesion and migration. Repurposing of these FDA-approved drugs provides an advantage over new chemical entities that require safety testing prior to clinical application, thereby offering the potential for rapid translation to the clinic. This study has completed a Phase I clinical trial, and results are in progress.

Dr. Laurie Hudson, University of New Mexico Health Sciences Center

GAP 4 & GAP 5

Virus-based Toxin Delivery for Ovarian Cancer Tumors

Investigated the use of a virus engineered to deliver toxic therapy to ovarian tumors. This virus can specifically attach to ovarian cancer cells and deliver a toxic gene that will kill the cells. The goal is to develop this technology into an alternative treatment method for patients.

David T. Curiel, Washington University, St. Louis

GAP 6

Recruit and retain outstanding scientists for a lifetime career as ovarian cancer researchers

GAP 4 & GAP 5

Using MSC1 Immunotherapy to Create an Anti-tumor Response

Identified an anti-tumor MSC1 therapy as a novel cancer immunotherapy. This therapy safely and effectively re-trains the immune system to switch from a pro-tumor state to an anti-tumor state, slowing the progression of ovarian cancer.

Aline Betancourt, Tulane University

GAP 4 & GAP 5

Targeting Tumor Vasculature to Eliminate Ovarian Cancer Cells

Supported research leading to a patent for an immunotherapy drug, now in Phase I clinical trials. This immunotherapy drug uses antibodies to eliminate TEM1, a critical factor for tumor vasculature. Results from this clinical trial are forthcoming.

George Coukos, University of Pennsylvania

GAP 6

The Ovarian Cancer Research Academy

Founded in FY09, the Ovarian Cancer Academy is a unique and innovative virtual community that provides outstanding early-career investigators (ECIs) with intensive mentoring, national networking, a peer group, and a collaborative research environment. The goal is to develop successful, productive scientists and foster in them a lifelong commitment to ovarian cancer research. To date, the 17 current and former Academy ECIs in laboratories across the U.S. have produced 237 publications, 153 presentations, and obtained nearly \$14M in external ovarian cancer research grants.

Nita Maihle, Georgia Regents University

Research on the Horizon

The Ovarian Cancer Consortium for Long-Term Survival

Although the overall survival statistics for ovarian cancer are dire, women survive for many years, even decades, following treatment. The DoD OCRP funded two Consortia for Long-Term Survival to figure out why. The Multidisciplinary Ovarian Cancer Outcomes Group (MOCOG) comprises a highly experienced, international team of Ovarian Cancer Association Consortium (OCAC) researchers. This team is studying 600 long-term and 600 moderate-term (5- to 7-year) survivors of advanced-stage, high-grade serous ovarian cancer (HGSOC), working backwards to analyze immune, genomic and epidemiological factors as well as clinical and lifestyle characteristics that impact their survivorship in comparison to short-term (2- to 4-year) survivors. A second research team is working towards analyzing data to predict short-term versus long-term survival for patients with early-stage HGSOC. These outcomes will be analyzed to help design individualized treatment plans for ovarian cancer patients, to achieve the most benefit for those who exhibit short-term survivor characteristics. The results of this project will also create an invaluable resource of genomic/biologic/proteomic data that is linked to quality of life and clinical data.

Malcolm Pike, Memorial Sloan Kettering Cancer Center; Michael Birrer, Massachusetts General Hospital

Chemotherapy-Induced Cognitive Impairment: A Novel Prospective Study

Patients who receive chemotherapy for ovarian cancer sometimes experience a phenomenon called “chemobrain,” a side effect of therapy that affects memory, attention, information processing, and thought organization. A clinical trial is currently enrolling ovarian cancer patients to understand chemobrain, to assist physicians in timely diagnosis of

this condition and delivery of treatment to alleviate symptoms. This DoD OCRP project brings the important survivorship issue of “chemobrain” to the forefront.

Rachel Miller, University of Kentucky

A New Anti-Diabetes Drug as a Novel Therapy for Epithelial Ovarian Cancer

An existing drug, Sitagliptin (Januvia™), commonly prescribed to treat type II diabetes, may prove to be a novel therapy for epithelial ovarian cancer. Researchers identified a protein called “CXCL10,” normally a strong signal for white blood cells to infiltrate and attack tumor tissue, that is modified in HGSOCs. Another protein called DPP4 mediates this modification, causing CXCL10 to act as an “off switch,” shutting down the anti-tumor immune response. Because Sitagliptin targets DPP4, researchers are testing whether it will work in combination with standard chemotherapy to treat HGSOC in a mouse model. If successful, this new regimen could provide renewed hope to ovarian cancer patients.

Magdalena Plebanski, Monash University, Australia

Untapped Therapeutic Targets in the Tumor Microenvironment

Changes in the microenvironment surrounding a tumor can significantly affect how the cancer grows and behaves. One specific type of change, the formation of carcinoma-associated fibrosis (CAF), is the subject of intense study. DoD OCRP researchers are investigating whether preventing the development of CAFs will slow tumor growth. They are repurposing anti-fibrotic agents currently in clinical trials to test their effectiveness in a pre-clinical mouse model of ovarian cancer, providing important data for the use of such agents in human patients. This team is also studying how the genes affecting the stroma/extracellular matrix are associated with metastasis, recurrence, and poor survival. They are working to

develop a genetic test that can be used to identify ovarian cancer survivors who are most likely to experience early relapse.

Sandra Orsulic, Cedars-Sinai Medical Center

Therapeutic Strategies against Cyclin E1-Amplified Ovarian Cancers

A collaborative effort within the DoD OCRP Ovarian Cancer Academy is using novel strategies against a type of ovarian cancer harboring “Cyclin E1 (CCNE1) amplification,” which occurs in about 20% of HGSOCs. Patients with HGSOC typically do not respond well to platinum-based chemotherapy or PARP inhibitors, resulting in a poor outcome. The team is using pre-clinical animal models to test various agents that inhibit specific aspects of CCNE1 biology, to develop new treatment strategies for patients diagnosed with HGSOC.

Panagiotis Konstantinopoulos, Rugang Zhang, and Dipanjan Chowdhury, Dana-Farber Cancer Institute

A Paradigm Shift for Ovarian Cancer Detection: Screening Liquid-Based Pap Tests by Mass Spectrometry

Ovarian cancer is difficult to detect before reaching late stage. DoD OCRP researchers are working to change this by developing a non-invasive screening test that can be readily incorporated into a routine Pap test, allowing women to simultaneously receive screening for ovarian and cervical cancer. Using Mass Spectrometry to analyze the Pap test, they are focused on identifying peptides and proteins that are unique or significantly elevated in women with early-stage ovarian cancer, compared to the general population. If sufficient sensitivity and specificity can be achieved with this new test, it would be a game-changer for women’s health.

Amy Skubitz, University of Minnesota, Twin Cities

Novel Platinum/Taxane-Based Drug Combinations for Ovarian Cancer

In a high-risk/high-reward Pilot award, DoD OCRP researchers are testing Fenretinide (4-HPR), an anticancer drug based on vitamin A, in combination with other anti-cancer drugs against patient-derived intraperitoneal ovarian cancer xenograft animal models. This team

has developed a novel formulation of 4-HPR, which allows for higher plasma levels of the drug, and provides promising novel approaches to treatment of recurrent ovarian cancer.

Charles Reynolds, Texas Tech University Health Sciences Center, Lubbock

Organizing the Cellular and Molecular Heterogeneity in High-Grade Serous Ovarian Cancer by Mass Cytometry

Each subtype of ovarian cancer has its own unique molecular signature. Understanding these differences is the key to matching the right treatment to the right tumor and maximizing patient benefit. This innovative research is analyzing a single cell with a technology called mass cytometry, which simultaneously measures protein expression, protein function, and molecular signatures of primary ovarian cancer samples. To date, work on this project has identified a “common family tree” of HGSOC from different patients. This novel approach could lead to new methods for early detection as well as a deeper understanding of the disease in order to develop personalized treatment regimens.

Gary Nolan, Stanford University

Prevention of Ovarian High-Grade Serous Carcinoma by Elucidating Its Early Changes

HGSOC is one of the deadliest types of ovarian cancer. A multi-organization collaboration is working to identify and characterize the early changes that lead to its development. The researchers demonstrated that an early lesion in the fallopian tube called “serous tubal intraepithelial carcinoma (STIC)” is the precursor of HGSOC, and they developed and validated a publically available algorithm for the diagnosis of STIC. They are now assessing whether STIC characteristics can be modified, to potentially prevent HGSOC. In addition, they have shown that treatment with ovastatin significantly reduced STIC development and subsequent ovarian tumor growth in an animal model.

Robert Kurman, Johns Hopkins University