Ovarian Cancer Research Program

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) has transformed the landscape of ovarian cancer research to the benefit of patients everywhere. Our overarching goals are:

- Understanding the precursor lesion/stem cell, microenvironment, and pathogenesis/progression of all types of ovarian cancer, including rare subtypes
- Developing or improving the performance and reliability of screening, diagnostic approaches, and treatment
- Developing and validating models to study the initiation and progression of ovarian cancer
- Addressing issues in primary prevention and survivorship
- Investigating tumor response to therapy, including tumor survival, dormancy, cell death, clonal evolution, and tumor heterogeneity
- Enhancing the pool of ovarian cancer scientists

The success of the OCRP can be attributed to the synergistic efforts of many talented and dedicated individuals. A hallmark of the OCRP is the partnership of ovarian cancer survivors and advocates with scientists and clinicians, all of whom work together to set program priorities, conduct peer review of research proposals, and identify high-impact, innovative research that will lead to the elimination of ovarian cancer. More than 500 ovarian cancer survivors and advocates, scientists, and clinicians have participated in the OCRP. The disease survivors and advocates bring their unique perspective and the human dimension of the disease into the OCRP's policy, investment strategy, and research focus to encourage funding recommendations that reflect the concerns of ovarian cancer advocates and their families, as well as the clinicians who treat them.

The DoD OCRP was established in 1997 to define and address the critical research gaps facing the ovarian cancer community. The 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 $256 million (M) in Congressional appropriations between fiscal year 1997 (FY97) and FY15, the OCRP has funded 346 research awards, resulting in over 1,370 peer-reviewed publications, over 100 patent applications, and high-impact advances in the prevention, screening, diagnosis, and treatment of ovarian cancer.

GAP 1 & GAP 2

New Models to Study the Effect of BRCA1 on Ovarian Cancer

Developed a new mouse model that deleted the BRCA1 gene from ovarian cells. This gene 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, as well as 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 the 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 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 endometriod ovarian adenocarcinoma were developed and provide invaluable insight into the pathogenesis of ovarian cancer, testing of molecular therapies, and development of 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 and HER2 are similar between human 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

GAP 3
Increase prevention and improve quality of life for survivors

GAP 4
Devise and advance new and improved techniques to diagnose and treat ovarian cancer

GAP 5
Investigate tumor response and/or resistance to treatment

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 a 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@fccc.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 of the disease. As a result, genetic testing guidelines in Australian 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, as well as 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) lesions, which are precursors 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, both 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 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 Food and Drug Administration (FDA) and is the only approved blood test to help determine whether 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 pilot clinical trial and is now in Phase I testing.

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 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 retrains 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

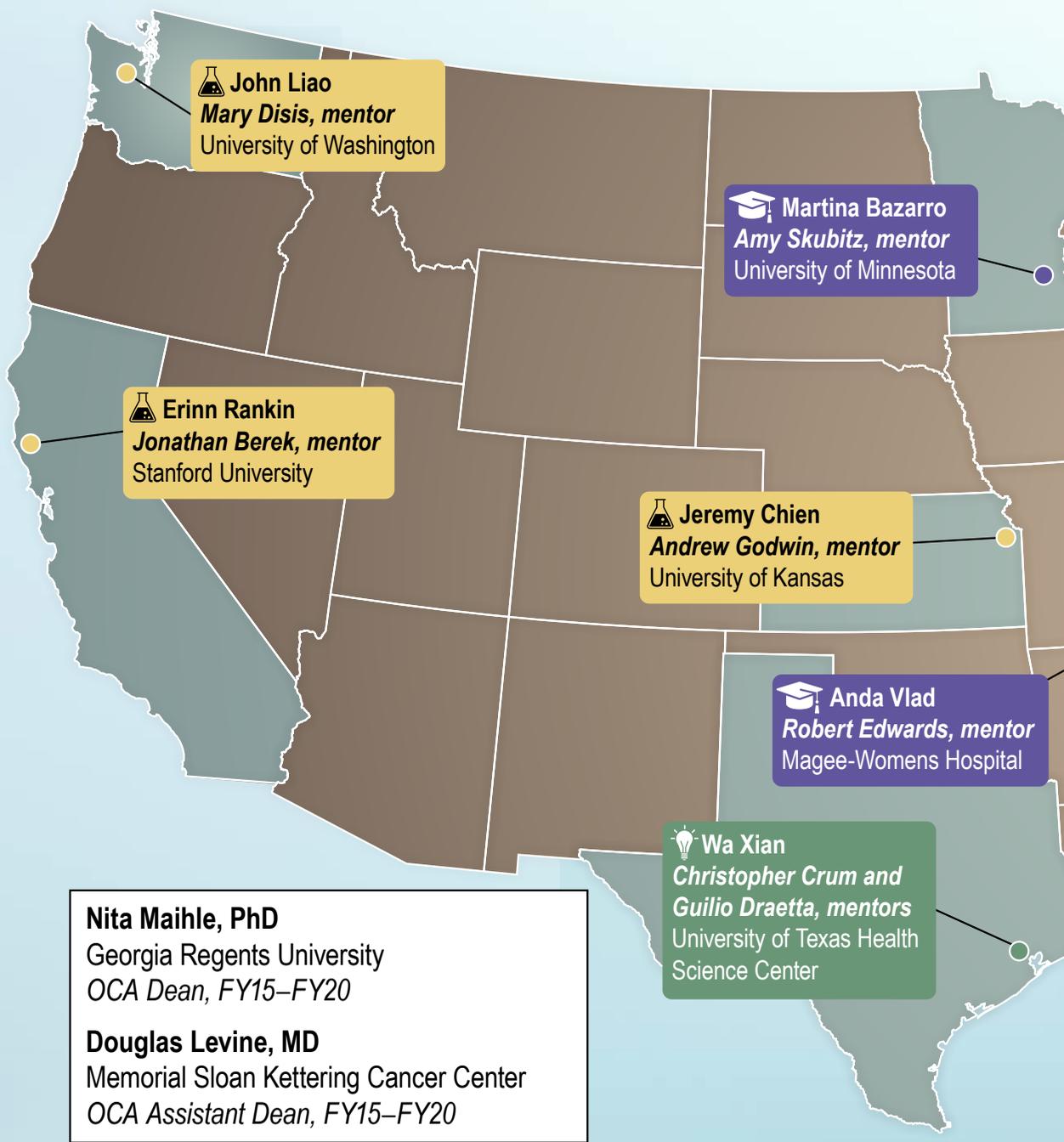### Targeting Tumor Vasculature to Eliminate Ovarian Cancer Cells

Supported research leading to a patent for an immunotherapy drug, which is 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

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

The Ovarian Cancer Research Academy

Founded in FY09, the Ovarian Cancer Academy (OCA) 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 19 current and former Academy ECIs in laboratories across the United States have produced 362 publications and 198 presentations, and have obtained nearly $23M in external ovarian cancer research grants.

John Liao
Mary Disis, mentor
University of Washington

Martina Bazarro
Amy Skubitz, mentor
University of Minnesota

Erinn Rankin
Jonathan Berek, mentor
Stanford University

Jeremy Chien
Andrew Godwin, mentor
University of Kansas

Anda Vlad
Robert Edwards, mentor
Magee-Womens Hospital

Wa Xian
Christopher Crum and Guilio Draetta, mentors
University of Texas Health Science Center

Nita Maihle, PhD
Georgia Regents University
OCA Dean, FY15–FY20

Douglas Levine, MD
Memorial Sloan Kettering Cancer Center
OCA Assistant Dean, FY15–FY20

🧪 **Karen McLean**
Ronald Buckanovich, mentor
University of Michigan

🎓 **Panagiotis Konstantinopoulos**
Alan D'Andrea, mentor
Dana-Farber Cancer Institute

🧪 **Geeta Mehta**
Ronald Buckanovich, mentor
University of Michigan

🧪 **Elizabeth Poole**
Shelly Tworoger, mentor
Brigham and Women's Hospital

💡 **David Pepin**
*Patricia Donahoe and
Michael Birrer, mentors*
Massachusetts General Hospital

🎓 **Kathryn Terry**
Daniel Cramer, mentor
Brigham and Women's Hospital

🧪 **Dmitriy Zamarin**
Carol Aghajanian, mentor
Memorial Sloan Kettering
Cancer Center

🧪 **Anirban Mitra**
Kenneth Nephew, mentor
Indiana University

🧪 **Yang Yang-Hartwich**
Gil Mor, mentor
Yale University

🧪 **Juan Cubillos-Ruiz**
Jose Conejo-Garcia, mentor
Cornell University

🎓 **Rugang Zhang**
Dario Altieri, mentor
Wistar Institute

🎓 **Charles Landon**
Ronald Alvarez, mentor
University of Virginia

🧪 **Neil Johnson**
Jeff Boyd, mentor
Fox Chase Cancer Center

Providing Hope: Increasing Long-Term Survivorship of Ovarian Cancer Patients

Malcolm Pike, Ph.D., Memorial Sloan-Kettering Cancer Center
Photo by permission of Dr. Malcom Pike.

Michael Birrer, M.D., Ph.D., Massachusetts General Hospital
Photo by permission of Massachusetts General Hospital.

Patients diagnosed with ovarian cancer today face a difficult reality: with an overall 5-year survival rate of just 45%,[1] ovarian cancer is the deadliest gynecologic cancer. Yet amid the uncertainty and apprehension of diagnosis, there is hope. To improve the prognosis for those with ovarian cancer, the OCRP offered the Outcomes Consortium Development Award in FY12 to lay the groundwork for a new, multi-institutional research effort to identify and understand specific predictors of disease outcomes in ovarian cancer patients. A subset of patients diagnosed with ovarian cancer become long-term survivors (over 10 years survival from their date of diagnosis); the consortium was aimed at building teams of talented researchers who would work to discover what differentiates these patients from the others. In FY15, the OCRP offered the Outcomes Consortium Award as the second stage of this effort with the goal of advancing the consortia from the development phase to the research phase. Two teams, one led by Dr. Malcom Pike and the other by Dr. Michael Birrer, were chosen to receive the FY15 Outcomes Consortium Award to support their efforts to identify predictors of long-term survival and to enable physicians to tailor therapies to individual patients to increase their survival and quality of life.

The Multidisciplinary Ovarian Cancer Outcomes Group (MOCOG), led by Dr. Pike at Memorial Sloan Kettering Cancer Center, is working with patients with advanced-stage, high-grade serous cancer, which accounts for over 80% of ovarian cancer deaths. They will investigate the role of the patients' immune response; their genetics, especially those related to DNA repair; and epidemiological and lifestyle factors that contribute to long-term survival. The MOCOG is a collaboration of 10 international sites that will leverage samples, data, and techniques to search out novel immune therapy approaches to ovarian cancer treatment and identify the patients who would benefit from these targeted immune therapies.

The Ovarian Cancer Consortium for Long-Term Survival, led by Dr. Birrer at Massachusetts General Hospital, focuses on finding predictive biomarkers that will aid in the design of individualized care for ovarian cancer patients. With the majority of ovarian cancer patients succumbing to this progressively chemo-resistant disease, this international consortium, comprised of nine sites, will work to determine the characteristics of long-term survivorship by investigating both patients and their tumors. They will gather genomic, proteomic, and biologic data, as well as environmental and quality of life data, to identify novel therapeutic targets and biomarkers for the early detection of ovarian cancer and to develop and identify tailored therapies for those patients.

The highly focused studies and combined efforts of the world's leading investigators in these consortia will have a major impact on understanding the predictors of outcomes in ovarian cancer that will ultimately and significantly accelerate progress toward long-term survivorship. Their efforts are integral to the OCRP's mission to support patient-centered research to prevent, detect, treat, and cure ovarian cancer. Research supported by the OCRP continues to provide hope that one day all women diagnosed with ovarian cancer will become long-term survivors.

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[1] *American Cancer Society, 02/04/2016*

Pathway of Discovery to a Cure

Patents Created by OCRP Investigators

Use of modified Herpes Simplex Virus – 2 (HSV) as a cancer therapy
HSV-2 with a fusogenic activity (FusOn-H2) as a cancer therapy. The Principal Investigator (PI) has two National Institutes of Health (NIH) grants totaling $3.5M to perform clinical trials on solid tumors. *Xiaoliu Zhang (Patent No. 8,986,672)*

Enzyme-mediated tumor imaging and therapy
Prodrugs that can be used to detect solid tumors and then deliver drugs directly within the tumor. The technology has been licensed to Sabik Medical, Inc. *Amin Kassis (Patent No. 9,320,815)*

Vaccines against tumor vascular markers
MORAb-004 has been part of three completed Phase 1 and two completed Phase 2 clinical trials. MORAb-004 is licensed by Morphotech, Inc., and is now called Ontuxizumab. *George Coukos (Patent No. 9,290,556)*

Detection of cancer by elevated levels of BCL-2
Detection and monitoring of ovarian cancer by testing elevated Bcl-2 levels in the urine. This technology was purchased by Ovation Diagnostics and is preparing for clinical trials. *Patricia Kruk (Patent No. 8,034,549)*

Compounds for targeting cancer stem cells
This patent is for chemical compounds that can be used as therapeutic agents against cancer stem cells. The PI received an NIH Probe Development Award with funding to start June 2017. *Ronald Buckanovich (61,730,832 patent pending)*

Cell lines for the continuous production of alphavirus vectors
Sindbis viral vectors can be used to deliver cancer gene therapy. This technology has been purchased by CYNVEC and their first drug candidate, CYN-101, is designed to treat ovarian cancer. *Daniel Meruelo (Patent No. 7,378,272)*

Use of Elafin to detect ovarian cancer
Detecting ovarian cancer using the Elafin polypeptide as a biomarker. The Elafin polypeptide has been shown to correlate with poor outcomes in high-grade serous ovarian cancer. *Michael Seiden, Ronny Drapkin (Patent No. 8,486,648)*

Clinical Development

Salpingectomy to reduce ovarian cancer mortality
First federally funded study exploring the Fallopian tube as a possible source of ovarian carcinoma, which led to a paradigm shift in the understanding of ovarian cancer. *OC073389, Elizabeth Swisher*

Recommendations on genetic testing and clinical stratification.
2,000 patient study identifying the genetic underpinnings of ovarian cancer that led to the recommendation for genetic testing of women and the stratification of women in clinical trials, based on their genetic profile. *OC120312, Elizabeth Swisher*

Accelerated FDA approval for rucaparib and companion diagnostic CDxBRCA
Data from the PI's Synergistic Translational Leverage Award was used to support accelerated FDA approval of rucaparib for women with ovarian cancer. *OC120506, Elizabeth Swisher*

Understanding non-BRCA hereditary risk in African-American women
The hereditary risk of BRCA1 and BRCA2 mutations in African-American (AA) women isn't fully known. This work will be used for improving access to care and genetic testing of AA women. *OC140243, Elizabeth Swisher*

Clinical Trials

Statins and improved survival
Statins are shown to inhibit HMGCoA reductase and are being tested to determine whether the administration of statins in women can show anti-tumor effects. *OC130622, Kala Visvanathan*

AIM & response prediction
AIM (AZA Immune gene set) is a set of biomarkers used to predict and monitor epigenetic therapy in advanced ovarian cancer. *OC130454, Stephen Baylin*

JO-1 improves drug penetrance
The protein JO-1 can open the tight junctions that hold cancer cells together, allowing chemotherapies to advance further into the tumor. *OC110283, Andre Lieber*

mAGIC App to encourage genetic counselling
The overall study objective is to develop and assess the feasibility and effectiveness of a theory-based intervention aimed to encourage ovarian cancer survivors to receive genetic counseling. *OC130444, Melissa Geller*

Impact of the DoD OCRP

The OCRP 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
- mAGIC App to Encourage Genetic Counseling
- 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

- Using NSAIDs to Treat Ovarian Cancer
- Using Statins to Treat Ovarian Cancer
- Targeting Tumor Vasculature to Eliminate Ovarian Cancer Cells
- Using MSC1 Immunotherapy to Create an Anti-Tumor Response
- Using Viruses to Deliver Toxins to Treat Ovarian Cancer Tumors

New Research Tools

- New Model to Study the Effect of BRCA1 on Ovarian Cancer
- 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: Recruit and Retain Outstanding Scientists

Research on the Horizon

Combining PARP Inhibitors with GLS1 Inhibitors to Treat Resistant Ovarian Cancer

The PARP inhibitor, olaparib, is FDA-approved to treat platinum-resistant ovarian cancer in women with BRCA mutations. The majority of ovarian cancer patients do not have these mutations; for them, olaparib is rarely effective.

- Clinical trial will test combining olaparib with another kind of drug, called an GLS1 inhibitor, in women without BRCA mutation.
- Scientists believe GLS1 inhibitors will create conditions similar to BRCA mutation, making the PARP inhibitors effective.
- **Impact:** New treatment strategy could extend effective PARP inhibitor therapy to a much larger population of ovarian cancer patients.

Michael Birrer, Massachusetts General Hospital

New Imaging Biomarker to Predict Benefit of PARP Inhibitors

PARP inhibitors can sometimes be an effective treatment for ovarian cancer patients who do not have BRCA mutations, but it is very difficult to identify which ones will benefit.

- Investigates a new molecular imaging biomarker to non-invasively measure PARP levels inside ovarian cancer cells.
- Could be used to identify women whose tumors are likely to respond to PARPi therapy, so that women take the drugs that are most likely to help.
- Could allow providers to switch women to alternative therapy months sooner.
- **Impact:** Could form the basis for image-guided chemotherapy.

Fiona Simpkins, University of Pennsylvania

Making Chemotherapy More Effective and Less Toxic

In a previous OCRP award, this investigator discovered the protein JO-1 can open the tight junctions between cancer cells, allowing chemotherapies to advance further into the tumor.

- New award supports a Phase I trial to combine JO with the chemotherapy drug, Doxil, in platinum-resistant ovarian cancer patients.
- Could make Doxil more effective by increasing tumor cell exposure and less toxic by requiring fewer sessions and/or lower dosage.
- **Impact:** New approach meets the urgent need to address recurrence and overcome resistance to present therapies.

Andre Lieber, University of Washington

Enhancing Immunotherapy with Epigenomic Priming

Ovarian cancer tumors evade detection by the body's natural immune system. A better understanding how this happens could unlock an entire new class of much-needed therapies.

- Tests the hypothesis that tumors use DNA methylation to hide from the immune system.
- Combines drugs that block DNA methylation with immunotherapy agents, potentially making the cancer cells more recognizable.
- **Impact:** Could unlock an entire new class of much-needed therapies for women with poor prognosis who are experiencing relapse.

Daniela Matei, Northwestern University

Chemotherapy-Induced Cognitive Impairment: A Novel Prospective Study

"Chemobrain" is a side effect of chemotherapy experienced by some ovarian cancer patients. It affects memory, attention, information processing, and thought organization.

- This clinical trial is currently enrolling ovarian cancer patients to understand chemobrain.
- The goal is to assist physicians in timely diagnosis and delivery of treatment to alleviate symptoms.
- **Impact:** Brings an important survivorship and quality of life issue to the forefront of ovarian cancer research.

Rachel Miller, University of Kentucky

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

Sitagliptin, a drug that is commonly prescribed to treat Type II diabetes, targets a protein that has been shown to be important in epithelial ovarian cancer.

- A protein called DPP4 is involved in throwing the cellular "off switch" that shuts down the anti-tumor immune response.
- Sitagliptin targets DPP4, and researchers are testing its use in combination with chemotherapy to treat ovarian cancer.
- **Impact:** By repurposing an existing drug, this approach could rapidly advance a new treatment for women with epithelial ovarian cancer.

Magdalena Plebanski, Monash University, Australia

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

Early diagnosis is a key factor in ovarian cancer survival. Most patients (60%) are diagnosed in the deadly late stages.

- Developing non-invasive screening that can be readily incorporated into a routine Pap test.
- Uses mass spectrometry to identify peptides and proteins associated with early-stage ovarian cancer.
- **Impact:** Simultaneous screening for early-stage ovarian and cervical cancers would be a game-changer for women's health.

Amy Skubitz, University of Minnesota, Twin Cities

CDMRP
Department of Defense