Ovarian Cancer Research Program

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 $7.54 billion in appropriations from its inception through fiscal year 2013 (FY13). Funds for the CDMRP are added to the Department of Defense (DoD) budget in which support for individual programs, such as the Ovarian Cancer Research Program (OCRP), is allocated via specific guidance from Congress.

Application Review Process

The CDMRP uses a two-tier review process for application evaluation, with both tiers involving dynamic interaction between scientists and disease survivors. The first tier of 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, portfolio balance and composition, impact, and relevance to program goals.

Congressional Appropriations for the OCRP, FY97–FY13

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

Did you know?

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Ovarian Cancer Research Program
**Ovarian Cancer Research Program**

**History of the DoD OCRP**

The DoD OCRP began in 1997 with a congressional appropriation of $7.5 million (M). Since that time, the dedicated efforts of ovarian cancer advocates to increase public awareness of this disease and federal funding for its research have resulted in a total appropriation of more than $216M to the OCRP, including $20M in FY13.

The OCRP vision is adapted yearly to target critical research areas and to be responsive to the needs of the ovarian cancer community. Every year the OCRP evaluates the funding landscape by comparing research portfolios and award mechanisms of other federal and non-federal agencies and then develops novel award mechanisms to target the areas that are most critically in need. 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. The OCRP’s award mechanisms support complementary approaches to answer questions that are vital to the advancement of science, exemplifying the innovative and focused nature of this program.

**Long-Term Initiatives of the DoD OCRP**

- Understand precursor lesion/stem cell, microenvironment, and pathogenesis/progression of ovarian cancer
- Improve performance and reliability of disease markers and imaging toward screening and selecting the best therapeutic approaches
- Address issues in survivorship
- Enhance the pool of ovarian cancer scientists
- Investigate tumor response to therapy including tumor survival, dormancy, cell death, clonal evolution, and tumor heterogeneity

**Did you know?**

- World Ovarian Cancer Day, initiated in 2013, is May 8.
- Each year, nearly a quarter of a million women are diagnosed with ovarian cancer worldwide, and about 140,000 women die annually from the disease.
- Ovarian cancer causes more deaths than any other cancer of the female reproductive system.

**Dr. Molly Brewer, FY13 IP Chair, Carole and Ray Neag Comprehensive Cancer Center, University of Connecticut Health Center**

“One of the strengths of the OCRP and one of the exciting aspects of our approach is our ability to continually modify areas of focus as well as mechanisms of funding to meet new needs in the research community. Over the last few years, we have developed novel funding mechanisms, such as the Ovarian Cancer Academy and the Teal Innovator Award, to meet the needs of new investigators by providing funding, mentorship, and institutional support to induce the brightest young researchers to focus on ovarian cancer (Academy) and to attract excellent senior scientists to focus their research in ovarian cancer (Teal Innovator). The Integration Panel meets yearly to set goals and refine our approaches so we can build on our past successes and focus our resources on underfunded areas to improve the outcomes for women with ovarian cancer.”

**VISION**

Eliminate ovarian cancer.

**MISSION**

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

The significant impact of the DoD OCRP can be attributed to the collective wisdom and efforts of many talented and dedicated individuals. The partnership with the military, ovarian cancer survivors or consumer advocates, clinicians, and scientists brings together stakeholders that typically might not collaborate. Ovarian cancer consumer advocates serve as a voice for all survivors, providing a different perspective and helping scientists understand how the research will impact the ovarian cancer community. These partnerships 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.

• Ovarian cancer consumers have played a pivotal role in the establishment and impact of the OCRP.
• On a yearly basis, 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.
• More than 640 scientists and ovarian cancer consumers have participated in the OCRP’s two-tier review of research proposals.
• Consumer advocates and scientists participate as equal voting members during both peer and programmatic review of proposals.
• 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.

Making a difference. That’s what being a consumer reviewer means to me. Getting the chance to talk directly with researchers and having an impact on their views of how research affects women’s day-to-day lives means I’m giving back to my community. Research and clinical trials gave me 4 years of remission I know I wouldn’t otherwise have had. And when you have grade school children, every new day is precious.

~Kay Kerbyson, Ovarian Cancer TOGETHER! Inc.

Did you know?

• Age matters! Women younger than age 65 are about twice as likely to survive 5 years (56%) after diagnosis than women 65 years of age and older (27%).
Women living with ovarian cancer and survivors are so often relegated to the background because they have neither the time nor the strength to do more than survive. A small percentage have the drive to help their fellow travelers along the cancer journey. Serving on the ovarian cancer research panel is a rare privilege and the ultimate way to change the course of the disease for women yet to be diagnosed. The panel offers a forum where the voices of women living with ovarian cancer can inform and inspire the top researchers to greater innovation and more meaningful solutions to the recalcitrant enigma of ovarian cancer. It also inspires me and other consumer advocates to offer hope to our community of survivors that there are brilliant doctors and scientists worldwide who are dedicated to early detection, effective treatment, and even a cure for ovarian cancer.

~Betsy Garson Neisner, Cancer Connection, Inc.

When I filled out the paperwork to become a “consumer reviewer” for the DoD OCRP I had no idea what I was going to be doing! I was certainly nervous and a bit overwhelmed, having read all of my assigned proposals and the other panel proposals when I arrived in Reston to begin my first panel. I was so well cared for and encouraged by the program staff and scientists that I relaxed and then was amazed by what I learned and, more importantly, what I brought back home with me—knowledge about the disease I had and hope for myself and the many other women with ovarian cancer who I have had the privilege to meet since my diagnosis. I was able to tell them that there is a large group of scientists who are devoting themselves to finding an accurate diagnostic tool, new treatments, and ultimately a cure for ovarian cancer. This gives HOPE, something that women with ovarian cancer have not had the gift of before. I am so glad to have had the opportunity to represent so many women by being a part of this program!

~Anne Tonachel, Boston Medical Center

Did you know?

- Ovarian cancer is not a silent killer. In June 2007, a consensus statement outlining specific symptoms was released.
- Ovarian cancer symptoms include bloating, pelvic/abdominal pain, urinary symptoms, difficulty eating, or feeling full quickly.

Dr. Kathryn Terry, Academy Member, Brigham and Women’s Hospital

“Not only has the Academy provided the support I need to pursue the ovarian cancer research I’m passionate about, but it has created an incredible network of mentors and colleagues with remarkably diverse research interests considering we are all focused on ovarian cancer. As an epidemiologist studying risk factors that influence ovarian cancer risk on a population level, the opportunity to discuss ideas with ovarian cancer experts working in basic science and the clinic has been invaluable in moving my research forward.”
THE DoD OCRP TREK:
ADDRESSING UNMET NEEDS BY ESTABLISHING PRIORITIES, CRAFTING NOVEL AWARD MECHANISMS, AND SUPPORTING CUTTING-EDGE RESEARCH

The DoD OCRP fills unique niches by supporting high-impact research that addresses critical unmet needs in ovarian cancer. The DoD OCRP thinks differently—we create novel award mechanisms that focus on unmet needs and support synergistic efforts and nontraditional partnerships.

1997
Beginning of the DoD OCRP
» First DoD OCRP appropriation
» Ovarian cancer advocates launch grassroots campaign to increase research funding

Building Critical Ovarian Cancer Resources
» Focused on novel prevention strategies, etiology, early detection, preclinical therapeutics, and quality of life via Program Projects
» Established critical resources including ovarian cancer tissues and linked clinical data, and animal models
» Established critical, synergistic partnerships in the International OCAC* and the AOCS**
» Created the Resource Development Award to develop well-annotated tools for the research community

Bringing Talented Investigators into Collaborative and Interactive Ovarian Cancer Research Environments
» Developed junior faculty and transitioned independent researchers to ovarian cancer
» Supported HBCU/MI* investigators in developing research resources and careers
» Created the Ovarian Cancer Academy, an interactive, virtual mentoring and networking platform consisting of highly committed junior faculty with their mentors and an Academy Dean
» Offered a nested Teal Postdoctoral Scholar option to foster the next generation of ovarian cancer investigators through mentored research training

Ovarian Cancer Research Program FY97–FY12
Development of Ideas (by number of awards)

Translational Research: 13%
Collaborative Research: 4%
Innovators: 1%
Career Development: 16%
Concepts: 14%
Mature Ideas: 7%
Early Ideas: 45%

The OCRP’s current portfolio includes 284 awards made through 25 award mechanisms available over the past 16 years.

*Ovarian Cancer Association Consortium
**Australian Ovarian Cancer Study
***Historically Black Colleges and Universities/Minority Institutions
1999, 2002–2013  
**Supporting Innovative Research**
- Supported innovative, high-risk/high-reward research leading to critical discoveries driving the field forward
- Expanded or modified current thinking and approaches in ovarian cancer
- Supported two visionary leaders, the “Teal Innovators,” to focus their creativity on paradigm-shifting ideas in ovarian cancer

2007–2013  
**Translating Research**
- Supported innovative translational research to accelerate promising ideas toward clinical applications
- Created the Translational Leverage award mechanisms to maximize use of existing human-based ovarian cancer resources in translational research to amplify potential gains in knowledge
- Developed the Clinical Translational Leverage Award for studies that are adjunct or corollary to clinical trials

2007–2013  
**Leveraging Researchers and Resources**
- Supported the collaboration of investigators to investigate early disease changes in ovarian cancer through the Consortium Award
- Supported the collaboration of researchers to investigate early disease changes in ovarian cancer through the Consortium Award
- Promoted collaborative efforts to understand what is unique about long-term (>10 year) survivors through the Outcomes Consortium Development Award
- Created the Synergistic Translational Leveraging award mechanism for leveraging existing human-based ovarian cancer resources for maximum use beyond the original source

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**OCRP FY97–FY12 Portfolio Categorized by Research Area**  
(by number of awards)

- **Research Resources**: 14%
- **Biobehavioral Sciences**: 1.2%
- **Clinical & Experimental Therapeutics**: 18.6%
- **Detection & Diagnosis**: 9.6%
- **Primary Prevention**: 1.9%
- **Immunology**: 5.6%
- **Pathobiology**: 14%
- **Cell Biology**: 15.5%
- **Genetics & Molecular Biology**: 13.4%
- **Endocrinology**: 2.5%
- **Epidemiology**: 3.4%
- **Computational Biology**: 0.3%
Did you know?

- There is no early detection test for ovarian cancer. A Pap smear will NOT detect it.

**OCR: Accelerating Promising Ideas**

The FY13 OCRP continues to focus on innovative, high-risk/high-reward research that may lead to critical discoveries or major advancements through the Pilot Award, with the option of a nested Teal Postdoctoral Scholar to mentor postgraduate trainees in both basic and clinical ovarian cancer research. In addition, the Ovarian Cancer Academy Award will add new early-career investigators to the virtual academy that fosters rising stars in ovarian cancer research who are committed to sustained and productive careers in ovarian cancer research. FY13 will also see the return of the Teal Innovator Award, a mechanism that provides a visionary individual with the resources to pursue novel ideas with the potential to significantly reduce the burden from ovarian cancer.

There are two new award mechanisms for FY13 designed to maximize the utility of resources for the field and patient care. The Clinical Translational Leverage Award will support research projects that are adjunct or correlative to clinical trials to address high-impact research ideas or unmet needs in ovarian cancer. The Resource Development Award is designed to facilitate the development of a well-annotated, human-based resource with the goal of spurring transformative projects throughout the entire ovarian cancer research field.

**Developing and Leveraging Crucial Resources**

The OCRP helped establish partnerships to pool data and samples to gain the statistical power to find risk-associated genes and environmental and lifestyle risk factors. The Program Projects helped build some of the databanks being used to elucidate familial risk and provide the crucial samples and clinical data needed to tease apart the different subtypes of ovarian cancer. Recognizing that ovarian cancer resources are often confined to investigators’ labs where they were first developed and are not always available for use by other investigators, the OCRP continues to offer leveraging mechanisms designed to maximize the utility of existing resources.

"In order to advance our studies in cancer research I think we all understand that we have to be willing to share. The model of a single laboratory scientist sort of working away alone doesn't really work anymore. If we want to make meaningful progress we have to be willing to share our mouse models. We have to be willing to share our human-based resources."

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**Dr. Denise Connolly, Fox Chase Cancer Center**
**Cultivating Talented Investigators in Ovarian Cancer Research**

Building a critical mass of dedicated, career ovarian cancer researchers is essential to eliminating ovarian cancer. The OCRP has funded investigators at the trainee and junior faculty levels through mechanisms designed to develop ovarian cancer researchers within their individual institutions. In contrast to traditional training awards, the Ovarian Cancer Academy is a unique, virtual academy providing intensive mentoring, national networking, and a peer group for junior faculty in a collaborative and interactive environment.

**Fostering Innovative, High-Impact Research**

The OCRP offers mechanisms that support conceptually innovative, high-risk/high-reward research that could ultimately lead to critical discoveries or major advancements that will provide new paradigms, technologies, molecules, or applications that will drive the field of ovarian cancer research and patient care.

**Facilitating Collaborative Partnerships**

Recognizing that research collaborations are important in investigating the increasing complexity of disease, the OCRP developed “Team Science” award mechanisms that bring together the most talented scientists from different disciplines and organizations to solve a problem. Such collaborations can result in a level of productivity that is greater than that achievable by each scientist working independently. These collaborations then help unravel complex phenomena, and significantly accelerate progress.

**Pushing for Translation to Patient Care**

Given the program’s vision to eliminate ovarian cancer, the OCRP has offered award mechanisms dedicated to cutting-edge research designed to move successful laboratory results to a patient setting and vice versa. Translational research spans the continuum from discovery of a target to clinical trials, and the OCRP funds research projects at nearly every stage.

**Did you know?**

- Since the inception of the DoD OCRP, more than 140 ovarian cancer survivors have helped establish the OCRP’s priorities and research award mechanisms and have helped choose the research to be funded.
- September is Ovarian Cancer Awareness Month – Help raise awareness of the risks, signs, and symptoms of disease by wearing teal!
In FY09 the OCRP funded a virtual Ovarian Cancer Academy, which pairs early-career investigators (ECIs) with mentors established in ovarian cancer research. The Academy was designed to function as an interactive entity across institutional boundaries and aims to foster career investigators in ovarian cancer research whose dedication is critical to making significant strides toward the elimination of ovarian cancer. The first class of seven investigators was admitted with 5-year awards: Dr. Martina Bazzaro (University of Minnesota), Dr. Jeremy Chien (University of Kansas), Dr. Panagiotis Konstaninopoulos (Dana-Farber Cancer Institute), Dr. Charles Landen (University of Alabama at Birmingham), Dr. Kathryn Terry (Brigham and Women’s Hospital), Dr. Anda Vlad (University of Pittsburgh School of Medicine and Magee-Womens Research Institute), and Dr. Rugang Zhang (Wistar Institute). Academy Dean Dr. Patricia Donahoe (Massachusetts General Hospital) facilitates 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 making its mark as the original class takes strides toward career sustainability, with promotions, tenure, and additional grants awarded in the past 3 years. During this time the seven ECIs have made their mark on the ovarian cancer field by publishing 111 papers in ovarian cancer research and presenting 87 abstracts.

Members convened in Boston in March 2013 for their second annual meeting. They received feedback and advice on their current work from fellow Academy members and other mentors. Additionally, the ECIs participated at the subsequent joint symposium of the Dana-Farber/Harvard Cancer Center Breast and Gynecologic Cancer Programs.

The Academy is in the process of adding two new members, recommended in FY12: Dr. Geeta Mehta from the University of Michigan, who is designing and developing a three-dimensional model to mimic the ovarian tumor microenvironment in vitro (outside of the patient), and Dr. Elizabeth Poole from the Brigham and Women’s Hospital, who is examining psychosocial stress as a potential risk factor for ovarian cancer. 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.
**Academy Member – Clinician Scientist and Advocate**

**Dr. Charles Landen, University of Alabama at Birmingham**

The cancer stem cell hypothesis suggests that a subset of cells has the ability to initiate tumors, metastasize, and survive treatment. Ovarian Cancer Academy member Dr. Landen is intrigued by these cells, noting “The clinical course of ovarian cancer fits this paradigm. Most patients even with advanced disease will have an outstanding initial response to chemotherapy, even to the point where no disease is detectable by blood test, imaging, or even direct examination with surgery. However, even in the patients with strong initial responses, the majority will later develop recurrence with chemoresistant disease, leading us to believe that a very small portion of tumor cells have mechanisms in place that allow them to survive, lie dormant, and later regrow. If we can identify these cells and how they survive, it will significantly change our strategies on how to eliminate all cancer cells, not just the majority.” Dr. Landen is studying this hypothesis using several approaches, including analysis of stem cell signaling pathways, examination of patient samples prior to therapy as compared to recurrence, and direct implantation of tumors into mice so that responses of heterogeneous tumors to chemotherapy can be studied in a more controlled setting. Thus far, the research team has demonstrated that targeting either the Hedgehog pathway or the TGF-β coreceptor endoglin leads to enhanced ability of chemotherapeutic agents to kill chemoresistant cancer cells. Clinical trials to test these agents in patients are now under development. As a clinician, Dr. Landen is constantly inspired by his patients and is active in advocacy, serving on the Board of Directors for the Norma Livingston Ovarian Cancer Foundation in Birmingham and the national Foundation for Women’s Cancer. He says “We feel honored to be supported by the Department of Defense, given their history of considering patient advocates in their review process, and focusing on approaches that not only shed light onto the biology of disease, but also can ultimately lead to patient benefit.”

**FY12 Teal Innovator – Building Better Medicine**

**Dr. Paula Hammond, Massachusetts Institute of Technology, Koch Institute**

Often women with ovarian cancer have recurrent tumors that are highly resistant to standard therapies. While scientists learn the genetic signals that are involved in the survival of these cancer cells, we still need to develop ways to target these cellular processes. A strong potential candidate is short interfering RNA (siRNA), which can block very specific genes that enable cancer, but is difficult to deliver directly to tumors and is toxic at higher doses.

As a chemical engineer with a focus on polymers and materials science, I think about how nanomaterials can be designed for specific functions. My research group has recently examined methods of assembling materials that are inspired by nature. For example, we can take advantage of electrostatic interactions and generate nanoparticles in much the way a pearl forms around a particle of sand in an oyster, by starting with a core that contains a specific drug, and then “wrapping” siRNA with oppositely charged polymers around the core. Using this approach, a chemotherapy drug such as cisplatin can reside in the core of the nanoparticle and can be released after the genetic pathways that cause drug resistance are shut down by siRNA, thus leading to a “one-two-punch” approach to tumor therapy. We can design these nanoparticles to bind directly to tumor cells, lessening the significant and sometimes debilitating side effects caused by toxicity in healthy cells.

We are poised for major advancements in this field if we can merge the biological and medical knowledge gained on the genomic nature of the disease with an effective way to deliver more complex therapies that strategically combine genetic therapies with traditional chemotherapy and inhibitors. I also believe that new therapeutic approaches must combine clever biologically informed therapies while eliminating or lowering the potential for side effects in the patient. It is my vision to use a deeper understanding of cell biology and the pathology of ovarian cancer to generate biologically intuitive drug delivery systems tailored to address these challenges in ovarian cancer 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 risk factors of ovarian cancer and potential methods for prevention.

Genetic Modifiers of Ovarian Cancer Risk in BRCA1 Mutation Carriers

Dr. Fergus Couch, Mayo Clinic and Foundation

Mutations in the BRCA1 breast and ovarian cancer susceptibility gene have been identified in more than 10% of women who develop ovarian cancer, making BRCA1 the most common ovarian cancer predisposition gene. However, it is currently not possible to identify those mutation carriers who will go on to develop ovarian cancer in their lifetime and those who will not. Dr. Couch was awarded an FY09 OCRP 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 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. So far, the team has identified several novel modifiers of ovarian cancer risk for BRCA1 mutation carriers that can potentially be used for individualized ovarian cancer risk assessment once validated. With enhanced risk assessment tools, women at highest and lowest risk of ovarian cancer can be identified, and critical changes to their clinical care can be made.

DNA Modifications as Markers to Inform Ovarian Cancer Risk and Prevention

Dr. Eleanor Rogan, University of Nebraska Medical Center

Some of the most established risk factors for ovarian cancer include early age at menarche, late menopause, and nulliparity (never giving birth), highlighting a clear hormonal influence on the disease. Dr. Rogan hypothesizes that epithelial ovarian cancer is initiated by an imbalance in estrogen metabolism. “The resulting unbalanced estrogen metabolism,” she says, “can generate DNA damage and mutations that start the process leading to ovarian cancer.” Dr. Rogan received an FY09 Idea Development Award to explore this hypothesis by determining whether women with epithelial ovarian cancer form high levels of estrogen-DNA adducts that can be detected in urine samples and whether these levels are associated with polymorphic variants of key enzymes in the pathways of estrogen metabolism. Using urine samples collected from 34 women with ovarian cancer and 36 age-matched controls without cancer, she detected significantly higher levels of estrogen-DNA adducts in the samples with ovarian cancer. Further, the high ratio of estrogen-DNA adducts to estrogen metabolites and conjugates that she observed in samples from women with ovarian cancer indicated that estrogen metabolism was unbalanced in these women. The estrogen-DNA adduct ratio was found to be significantly associated with ovarian cancer, even after adjustments to account for other risk factors for the disease. Analysis of genetic polymorphisms revealed that women with one or two copies of the high-activity allele of CYP1B1 and two copies of the low-activity allele of COMT had significantly higher estrogen-DNA adduct ratios. Dr. Rogan says that the results of this study, “suggest that analysis of a urine sample for specific estrogen compounds can indicate whether a woman is at low or high risk for cancer or has the disease. In addition, these results suggest that rebalancing estrogen metabolism could reduce the risk of developing cancer.”
Previously believed to be a “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 for 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.

Identifying Imaging Targets
Dr. Charles Drescher, Fred Hutchinson Cancer Research Center

Despite improvements in treatment, ovarian cancer has proven very difficult to cure primarily because clinical diagnosis is frequently delayed until the cancer has spread outside of the ovary into the abdominal cavity. For over a decade, Dr. Drescher’s research group has focused on developing strategies for detecting ovarian cancer at an early stage when it is confined to the ovary and curable with currently available therapies. With funding from an FY09 Idea Development Award, the investigators are currently focusing on the identification of proteins that are unique to ovarian cancer cells. These proteins can then serve as targets for ovarian cancer detection and treatment. The long-term goal is to develop a noninvasive imaging test that can detect cancer when it is localized. Screening tests have led the investigators to several promising candidate biomarkers including folate receptor 1 (FOLR1), which is highly expressed in malignant ovarian tumors compared to benign ovarian tumors or normal ovary tissues, making it an ideal target for specific imaging of early ovarian cancer. With the help of collaborators, Dr. Drescher and his team have already started work in animal models to evaluate combining protein targets such as FOLR1 with next-generation imaging tests.

Identifying Genetic Changes Associated with Ovarian Cancer
Dr. Tian-Li Wang, Johns Hopkins University

In 2004, Dr. Wang was completing a postdoctoral fellowship in the cancer genetics lab of Dr. Bert Vogelstein. She was awarded a New Investigator Award by the FY04 OCRP to apply her expertise in cancer genomics to understanding ovarian serous carcinoma. By analyzing the number of gene copies in tumor samples, Dr. Wang identified Notch3 and Rsf1 as genes that had “extra” copies in high-grade serous carcinomas. Importantly, the extra copies of Rsf1 correlated with taxol resistance and poorer disease outcomes. Dr. Wang and her collaborator, Dr. Ie-Ming Shih, have continued to pursue the potential of Rsf1 as a prognostic marker and therapeutic target. Dr. Wang’s work indicates that the Notch3 pathway leads to aggressive forms of ovarian cancer, including chemoresistance.

Dr. Wang continues to research the genetics of different types of ovarian cancer, including ovarian clear cell carcinoma and low-grade ovarian serous carcinoma. She is a project leader in the FY10 OCRP consortium at Johns Hopkins University, where she is evaluating the potential of “oral contraceptives, commonly prescribed drugs, and DNA damaging agents that may alter molecular pathways in ovarian or fallopian tube epithelial cells” with an eye on identifying early generators of ovarian cancer and potential chemoprevention trials. Some of the genetic markers that Dr. Wang helped identify were recently used in a pilot study that used fluid from “Pap” tests to detect ovarian and endometrial cancers (Sci Transl Med, 2013). Dr. Wang notes “it is an example of bringing the research findings at the bench into clinical application… I believe that by promoting cross-talk and collaboration among researchers, clinicians, and patients, the translation of basic research findings to clinical applications can be expedited.” Her work continues to build on our understanding of ovarian cancer and open the doors to potential new therapies and preventions.
**Improving Diagnostics Throughout Patient Care**  
**Dr. Ralph Weissleder, Massachusetts General Hospital**

Despite increasing awareness of the broad molecular diversity in ovarian cancers, targeting tumor tissue according to its molecular characteristics is complicated by the understanding that tumor tissues can change at the molecular level from the time of initial diagnosis in response to treatment(s) or time. Conventional methods for interrogating molecular information require a sizeable tissue sample that can be impractical, costly, and potentially harmful outside of the initial debulking surgery. This makes it difficult to serially analyze how cancers are responding to treatment. Dr. Weissleder received an FY10 Translational Pilot Award to help overcome the sample size limitation for these analyses by adapting a device developed with his collaborator, Dr. Cesar Castro, for ovarian cancer. This diagnostic magnetic resonance (DMR) device uses a novel, multiplexed sensing technology that exploits magnetic resonance principles to detect molecular targets in ex vivo biological samples (those removed from a patient). This technology allows scientists to extract information about ovarian tumors from size-limited clinical samples such as fine needle aspirate, ascites, and even peripheral blood. The capability of the DMR to perform more comprehensive profiling using samples obtained from different sites obtained in a minimally invasive fashion may improve the ability to fully characterize tumors and predict responses to particular therapies. The DMR device under development is the size of a Kleenex box and allows for fully quantitative and operator-independent (i.e., not subjective) analyses within about 60 minutes. The device is run by and transmits results to a smart phone equipped with a customized application. If successfully adapted to work with ovarian cancer, this device could minimize the delay between biopsy of a suspicious lesion and pathology interpretation and allow diagnostic information to be obtained from blood or ascites samples. Furthermore, developing accurate and rapid point-of-care approaches would provide a timely snapshot of a tumor’s behavior, better equipping clinicians with relevant management options and treatment trajectories. Thus far, Dr. Weissleder has developed a preliminary diagnostic panel of proteins based on cell lines and tumor cells derived from ascites. These will be further tested on ascites and blood samples in an effort to improve short-term diagnostic testing. In continuously seeking to push the envelope by trying to make their devices smaller and chemistries more efficient and sensitive to aid the patient and clinician in the fight against the disease, the researchers envision the potential of their work to achieve exponential returns in the fight against ovarian cancer.

**A Novel Approach to Identify Early Markers of Ovarian Cancer**  
**Dr. David Lubman, University of Michigan**

The most significant prognostic factor in ovarian cancer is the disease stage at the time of diagnosis, with women diagnosed with early-stage I disease having about a 90% survival rate after 5 years. However, only about one-quarter of ovarian cancer cases are diagnosed as stage I due to the generality of early ovarian cancer symptoms and the lack of a rapid and reliable screening tool for the disease. The serum marker CA-125 is widely used in the diagnosis of ovarian cancer, but its effectiveness as a screening tool is limited by the fact that only about half of women with early-stage ovarian cancer have elevated CA-125 levels, and some benign conditions may cause elevations in CA-125 that are unrelated to ovarian tumors. Traditional biomarker screens that detect changes in protein concentration have failed to identify a sufficiently selective and specific biomarker for early-stage ovarian cancer. Dr. Lubman received an Idea Development Award in FY09 to apply a novel approach to biomarker discovery by examining protein glycosylation, a type of protein modification that has been reported to contribute to the pathogenesis of various cancers, in blood samples from women with benign tumors and early- and late-stage ovarian cancer. Through this work, Dr. Lubman has identified a panel of glycoprotein biomarkers that can be used to detect the presence of early-stage ovarian cancer from blood samples. Dr. Lubman has plans to validate these glycoprotein biomarker panels in a larger, independent set of blood samples from women with and without ovarian cancer. If successfully validated, the glycoprotein biomarker panels could be used in a simple blood test to screen for ovarian cancer.
Understanding Ovarian Cancer

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

Understanding the Extracellular Products of Tumors
Dr. Douglas Taylor, University of Louisville

Tumor cells have been shown to release membranous structures, called extracellular vesicles or exosomes, into the surrounding environment. These vesicles may express proteins derived from the originating cell. Dr. Taylor, recipient of an FY09 Idea Development Award, states that, “these tumor-derived extracellular vesicles not only represent a central mediator of the tumor microenvironment, but their presence in the peripheral circulation may serve as a surrogate for tumor biopsies, enabling real-time diagnosis and disease monitoring.” Dr. Taylor demonstrated that the level of extracellular vesicles in the blood of patients with cancer is three- to fourfold higher than in healthy controls. In addition, these tumor-derived extracellular vesicles have been shown to be extremely stable within circulation, making them attractive biomarker candidates. Analysis of high-throughput screening of microRNA signatures from the tumor-derived exosomes suggests that specific microRNAs are preferentially “sorted” into the vesicles, and some microRNAs are reflective of a malignant phenotype. Seeking to leverage the microRNA signatures of the exosomes, Dr. Taylor has identified some significant differences between early (stage I/II) and late (stage III) ovarian cancers, including the specific elevation of three microRNA species. In addition to evaluating the expression profiles of microRNA in exosomes, Dr. Taylor’s team has identified other types of RNA present in the vesicles that may “provide both diagnostic utility and insights into the ‘driver’ mechanisms of malignant transformation.”

Seeking the Origin of Ovarian Cancer
Dr. Christopher Crum, Brigham and Women’s Hospital

Serous cancer is a highly malignant disease that it is not often diagnosed until it has spread beyond the ovaries into the pelvic lining or peritoneum. To disrupt the progression of serous cancer, it is important to understand the origin of the tumor and whether it is preceded by a precancerous state. Recent studies have demonstrated that many early pelvic cancers in women originate in the fallopian tubes, not in the ovaries. Together with the description of a precancerous condition, called the p53 signature, in the fallopian tube, these findings are beginning to elucidate the origins of serous cancer. Dr. Crum received an FY09 Idea Development Award to further characterize this precancerous state and identify factors that increase the risk that the precancer will progress to malignancy. “The basis for the research question,” he said, “was my philosophy that many of the keys to cancer should be ‘visible’ in some form. We need only to notice them.” Dr. Crum identified an increase in expression of a transcription repressor that was associated with the transition from the p53 signature to malignancy, which may serve as a potential biomarker for malignant transformation. He has also demonstrated that patients with serous cancer have many more secretory

Did you know?

• About 5% to 10% of ovarian cancers are caused by the inherited mutation in BRCA1 or BRCA2 genes.

• Women with mutations in the RAD51D gene have a 1 in 11 chance of developing ovarian cancer (Nature Genetics, August 2011).

• Lynch syndrome, which is hereditary nonpolyposis colon cancer, is associated with an increased risk of developing ovarian cancer.
outgrowths, called SCOUTs, in their fallopian tubes than patients whose fallopian tubes were removed for benign lesions. Dr. Crum also isolated fallopian tube stem cells and observed that the cells from the normal fallopian tubes of patients with serous cancer had a higher rate of clonogenicity than from patients without cancer. Further, he began to characterize “keratin 5 clusters,” which share some morphological properties with SCOUTs, and he proposes they are stem cell outgrowths in the fallopian tubes. Dr. Crum, who continues his investigations into the origins of serous cancer, believes that, “…if we could determine what causes these benign changes and interrupt their development, we might also interrupt the process leading to pelvic serous cancer.”

**Understanding Early Changes That Lead to Ovarian High-Grade Serous Carcinoma**

**Dr. Robert Kurman, Johns Hopkins University**

The first Ovarian Cancer Consortium Award was awarded to Dr. Kurman’s group at Johns Hopkins University in FY10. The objective of this consortium is to develop a prevention strategy to reduce the burden of ovarian cancer, and therefore it focuses on definitively identifying and characterizing early tissue changes associated with the disease. This is being accomplished through four preclinical projects and an epidemiology project. The consortium is testing the hypothesis that a lesion in the fallopian tube called a serous tubal intraepithelial carcinoma (STIC) is the precursor of ovarian high-grade serous carcinomas, which account for a majority of ovarian cancer cases and related mortality. In shifting focus from early detection of cancer in the ovary to prevention of precursor lesions in the fallopian tube, it may be possible to significantly reduce incidence and mortality.

New data from the consortium regarding other early-stage precursors have emerged as the fallopian tubes are now being more carefully studied using a protocol that maximizes the available epithelium for review. Two forms of potential precursor lesions have been identified using this technique, tentatively designated “serous tubal intraepithelial lesions” (STILs, which are malformed cells that do not meet all STIC criteria) and “p53 signatures” (normal appearing epithelium that strongly expresses p53 and in which TP53 mutations have occasionally been identified). The consortium continues to evaluate these tissue changes to see if they are part of a normal reaction of surrounding tissue to malformations or if they are true precursors.

To date, the accomplishments of Dr. Kurman and his collaborators at Johns Hopkins University, the University of Toronto, Yale University, and Memorial Sloan-Kettering Cancer Center include: (1) Development and validation of an algorithm for the diagnosis of STICs (available at http://www.ovariancancerprevention.org/); (2) identification of a potential tissue biomarker (laminin γ1), which was more intense and diffuse in tested STICs compared to normal fallopian tube epithelium (American Journal of Surgical Pathology, 2012); and (3) demonstrating the utility of measuring the tissue expression of p53 as a surrogate for genetic tests for TP53 mutation in the histologic diagnosis of STIC (Journal of Pathology, 2012).

**Did you know?**

- Recent research indicates that the site of origin for high-grade serous ovarian carcinoma may be the fallopian tube.

**Judi Gordon, IP Member, SHARE**

“Today a lot of the proposals are looking at things that will be a new way to either identify ovarian cancer in its earliest stages or to treat ovarian cancer in a more targeted way that will actually treat the cancer and not harm the woman who is being treated.”
Evaluating the Effect of Fibroblasts on Ovarian Cancer
Dr. Rebecca Liu, University of Michigan

Sometimes the pursuit of an observation can lead to new understanding of disease and potential avenues of treatment. Historically, a shift in cancer treatment followed the simple observation that aggressive tumors have a more extensive blood supply, leading to the successful development of antiangiogenic therapies. Dr. Liu, an FY09 Idea Development Awardee, observed that, when compared to patients who responded well to chemotherapy, patients whose ovarian tumors appeared to be most resistant to treatment with chemotherapy contained a higher proportion of fibroblasts—a cell type that is characterized by its secretion of collagen—in the microenvironment that surrounds the tumor.

Dr. Liu hypothesized that ovarian carcinoma-associated fibroblasts (OCAF) can modulate both ovarian carcinoma cell growth and the response of tumors to standard chemotherapies. To confirm her observations in patients, she injected mice with different proportions of various fibroblasts with ovarian tumor cells. She found that mice treated with OCAF experienced significantly enhanced cancer growth compared to mice treated with other types of fibroblasts. To examine how OCAF might influence platinum chemoresistance in tumors, Dr. Liu repeated her studies, this time dosing the animals with cisplatin. She found that the presence of OCAF in both animal and cell assays inhibited ovarian carcinoma response to cisplatin, again not observed with other types of fibroblasts. This work demonstrates that OCAF cannot only promote ovarian cancer cell growth, but also inhibit chemotherapy-induced apoptosis in ovarian cancer cells.

Dr. Liu is currently investigating mechanisms of how these cell populations communicate and how to disrupt signaling between fibroblasts and ovarian cancer cells. She has partnered with a multidisciplinary team of researchers, including clinicians, molecular biologists, chemists, and biochemists, with the hope that they can develop new, more effective drugs targeted to different components of the surrounding, supporting cells. Of her collaborative team Dr. Liu says, “We believe that addressing problems from multiple perspectives is crucial in ‘out of the box’ thinking and for the design and implementation of new therapies for ovarian cancer.”

Did you know?

• Using estrogen alone as a postmenopausal hormone replacement therapy for 10 or more years increases the risk of ovarian cancer (Journal of the American Medical Association, July 2002).

• Using oral contraceptives for 5 or more years, pregnancy, or removal of ovaries and fallopian tubes lower a woman’s risk of developing ovarian cancer.
Treatment and Recurrence

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

Nanoparticle Delivery of a Suicide Gene for Ovarian Cancer Treatment

Dr. Janet Sawicki, Lankenau Institute for Medical Research

Dr. Sawicki received an FY05 Pilot Award to develop a locally administered gene therapy for advanced-stage metastatic ovarian cancer. Her long-term goal was to help effectively manage cancer for patients to live longer and healthier lives. Under this award, she tested the effectiveness of a nanoparticle that encodes a suicide gene, diphtheria toxin (DT-A). DT-A nanoparticle administered by intraperitoneal injection into mice with advanced ovarian cancer was able to effectively deliver DNA to tumors and was found to be well tolerated for up to 3 months. DT-A nanoparticle therapy, regulated by the MSLN gene promoter, also demonstrated reduced tumor growth rate, relative tumor size, and prolonged lifespan compared to control mice. Further studies by Dr. Sawicki showed that DT-A nanoparticle therapy was more effective at suppressing tumor growth than clinically relevant doses of cisplatin and paclitaxel. Dr. Sawicki has continued to make headway in advancing new therapies for ovarian cancer. She has continued to pursue this work and recently identified a nonviral vector that is better able to target delivery of these nucleic acids to tumor cells over healthy cells, thus reducing systemic toxicity. This advancement could greatly impact ovarian cancer patients and may provide treatment for metastatic cancer without the negative side effects of chemotherapy.

Toward Personalized Ovarian Cancer Therapy Through The Cancer Genome Atlas

Dr. Douglas Levine, Memorial Sloan-Kettering Cancer Center

The Cancer Genome Atlas (TCGA) Project was initiated in 2006 as a comprehensive and coordinated effort to define the important genomic changes involved in cancer. Using this large-scale resource of more than 500 ovarian carcinomas, Dr. Levine is working to translate findings from TCGA into a clinically useful panel of biomarkers that can provide “real-time” input into the prognosis and treatment of ovarian cancer patients. Ultimately, biomarkers found through these studies could be used to determine which targeted therapies will work best for which patients. Thus far, the investigators have identified markers representative of four transcriptome tumor subtypes that have been reported by TCGA. Dr. Levine has successfully used immunohistochemical staining to correlate tumor subtype to protein expression using BRCA1 as a test case as this mutation is well described and known to correlate with patient outcome. This simple staining assay could be used as an inexpensive initial screen to identify patients with BRCA1 dysfunction who may be triaged to undergo the more extensive BRCA1 germline mutation testing that is currently only offered to patients at high risk for hereditary breast or ovarian cancers. Dr. Levine and his team of investigators are continuing to identify proteins and corresponding signaling pathways that correlate with the genetic alterations in ovarian cancer as determined by TCGA with the hope of developing assays that can be used to predict clinical outcome and/or chemotherapy response for individual patients.
Identifying and Targeting Cancer Stem Cells  
Dr. Daniela Dinulescu, Brigham and Women’s Hospital

The mechanism underlying platinum chemoresistance in ovarian cancer is extremely complex; however, drug-resistant, self-renewing cancer stem cells are likely a major contributor to platinum-resistant disease left behind after current therapies that target the bulk of the rapidly dividing tumor cells. Successful elimination of ovarian tumors likely requires a combination therapy that affects both differentiated cancer cells and the initiating stem cell population. Dr. Dinulescu was awarded an FY09 Idea Development Award to study the role of cancer stem cells in tumorigenesis and treatment resistance. She developed a functional and molecular profile of ovarian cancer stem cells to identify both stem cell surface markers and key pathways critical for their function and discovered that the neurogenic locus notch homolog (Notch) cellular signaling pathway, and Notch3 in particular, play a key role in both cancer stem cell function and tumor resistance to platinum. Her preclinical studies have shown that a γ-secretase inhibitor, which inhibits Notch3, can deplete cancer stem cells and increase platinum sensitivity. Furthermore, these studies have shown that a combination therapy that includes platinum and a Notch pathway inhibitor significantly reduces cell viability and could potentially greatly improve disease outcome and long-term survival.

These results suggest important clinical applications for evaluating Notch expression and targeting as appropriate upon diagnosis or recurrence of ovarian cancer. As part of her ongoing studies, Dr. Dinulescu is focusing on identifying Notch transcriptional signatures using both patient and disease model samples. Such analyses will help identify markers of clinical interest to better classify which patients are most likely to benefit from γ-secretase inhibitor-based therapy. She says, “The overwhelming potential of Notch-based cancer treatments cannot be ignored. Increasing the use of personalized tumor biomarkers and translating these novel therapies into practice hold great promise for achieving a better prognosis in ovarian cancer.”

Dr. Johnathan Lancaster, H. Lee Moffitt Cancer Center and Research Institute at the University of South Florida

“The future of ovarian cancer hopefully lies in personalized medicine matching the right patient to the right drug using the biology of the individual patient’s tumor; we need to understand why ovarian cancers develop but also why they respond to some drugs and not others.”
**Animal Models**

Dr. Denise Connolly: *Mouse model with conditional BRCA1 and p53 knockout restricted to the ovary*

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

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

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

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

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

**Decision-Making Resources**

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

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

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*
Innovative Collaborations

Dr. Andrew Berchuck: **International Ovarian Cancer Association Consortium**, currently validating the finding from Dr. Bowtell’s Program Project that +331A allele of PR gene is significantly associated with protection against endometrioid 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 STICs.

Biomarkers

- **Dr. Martin McIntosh:** MMP7 elevated in serum up to 3 years prior to diagnosis of ovarian cancer.
- **Dr. George Coukos:** Panel of 13 promising genes as ovarian cancer biomarkers.
- **Dr. Samuel Mok:** New biomarkers for early-stage ovarian cancer: osteopontin, protease M, and lysophosphatidic acid.
- **Dr. Patricia Kruk:** Bcl-2 as a urinary biomarker for ovarian cancer.
- **Dr. Tian-Li Wang, Dr. Ie-Ming Sheh:** Rsf-1 as a prognostic indicator.

Tissues and Associated Clinical Data

- **Dr. Nicole Urban:** Repository with more than 6,000 individually identified ovarian tissue specimens.
- **Dr. Beth Karlan:** Human ovarian tissue and clinical database containing ovarian carcinomas (152) and benign ovaries (110).
- **Dr. David Bowtell:** Australian Ovarian Cancer Study, a multicenter, population-based resource involving the 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. Follow-up continues on about 1,000 women.
- **Dr. Santo Nicosia:** Ovarian cancer tissue repository with more than 600 samples.
- **Dr. Georgia Chenevix-Trench:** 1,839 ovarian epithelial and fibroblast cell samples (675 ovarian cancer cases and 1,164 controls).

Ovarian Cancer Research Program
In the Pipeline

Exceptionally promising early results in ovarian cancer research

**Dr. Fergus Couch – Identifying Genetic Modifiers of Ovarian Cancer Risk**
Identified several novel modifiers of ovarian cancer risk for women with BRCA1 mutations, including the 4q32.3 locus that is specific to these women.

**Dr. Andrew Berchuck – Ovarian Cancer Genetic Association Study and OCAC**
Founded the International Ovarian Cancer Association Consortium, which has recently 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.

**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).

**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. Laurie Hudson – Novel Therapeutic Strategy**
Characterized the FDA-approved R-enantiomer of naproxen, a nonsteroidal anti-inflammatory drug, as an inhibitor of small GTPase activation, epidermal growth factor receptor degradation, as well as ovarian cancer cell migration and invasion, making it a potential novel therapy for ovarian cancer metastasis.

**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. Thomas Walsh – Genetic Risk**
Confirmed that loss-of-function mutations in RAD51D predispose women without BRCA1/2 mutations to ovarian cancer but not breast cancer.

**Dr. Animesh Barua – Improving Detection**
Developing an early detection test for ovarian cancer using markers in the blood and non-invasive, tumor-targeted ultrasound imaging with enhanced resolution, using nuclear matrix proteins, interleukin-16-expressing tumor epithelium, and death receptor 6 as enhancing agents.

**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. David Bowtell and Gillian Mitchell – BRCA Mutations Without Family History**
Found that 44% of the 141 women with non-mucinous ovarian tumors carrying BRCA1/2 mutations did not have a family history of ovarian cancer or breast cancer.

**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 epithelial ovarian cancer, and loss of Wnt5a predicts a poor outcome in epithelial ovarian cancer patients.
Looking to the Future

**Dr. Elizabeth Swisher – Pilot Award**
Evaluating whether the Fanconi anemia DNA repair pathway can predict benefit from the addition of bevacizumab to combination chemotherapy.

**Dr. Shuang Huang – Pilot Award**
Evaluating the combination of phosphodiesterases 1C and 2A inhibitors as a means to treat metastatic ovarian cancers in a well-established mouse model.

**Dr. Jennifer Barton – Pilot Award**
Developing a miniature optical imaging device, called a falloposcope, to screen for ovarian cancer without general anesthesia or tissue incision.

**Dr. Amit Oza – Translational Leverage Award**
Partnering with experts in integrative computational biology and clinical research to develop new approaches to analyze basic ovarian cancer research findings faster and apply this knowledge to designing large-scale clinical trials.

**Dr. Brad Nelson – Teal Expansion Award**
Deciphering the adaptive immune response to ovarian cancer for future development of treatments to increase tumor immunity and patient survival.

**Dr. Robert Nussbaum – Translational Pilot Award**
Working to characterize BRCA1/2 variants of unknown significance to identify those that increase ovarian cancer risk.

**Dr. Victoria Bae-Jump – Pilot Award, Translational Pilot Award**
Investigating the metabolic and endocrine effects of obesity, and the importance of obesity time and duration during the lifespan, on the pathogenesis of ovarian cancer.

**Dr. Adam Karpf – Pilot Award**
Studying the role of BORIS activation, a gene recently identified as being upregulated in epithelial ovarian cancer, in causing epigenetic and genetic changes.

**Dr. Michael Birrer – Translational Leverage Award**
Identifying the genomic signature to stratify patients with early-stage ovarian cancer to predict those who will have a recurrence and benefit from chemotherapy from those patients who will not.

**Outcomes Consortium Development Award**
Understanding the subset of long-term (10+ years) survivors and identifying predictors for these women.

**Dr. Malcolm Pike – Elucidating predictors in patients with high-grade, advanced-stage serous ovarian cancer.**

**Dr. Anil Sood – Evaluating predictors in women with high-grade, and low-grade serous ovarian cancer.**

**Dr. Michael Birrer – Characterizing prognostic indicators in women with epithelial ovarian cancer.**

**Dr. Shia Izraeli – Pilot Award**
Using experts in the fields of cell signaling, centrosomal biology, and therapeutic use of RNA interference to characterize the centrosomal duplication protein STIL gene as a potential target for ovarian cancer therapy.
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usarmy.detrick.medcom-cdmrp.mbx.cdmrp-public-affairs@mail.mil
(301) 619-7071