CDMRP
Department of Defense

Defense Health Program

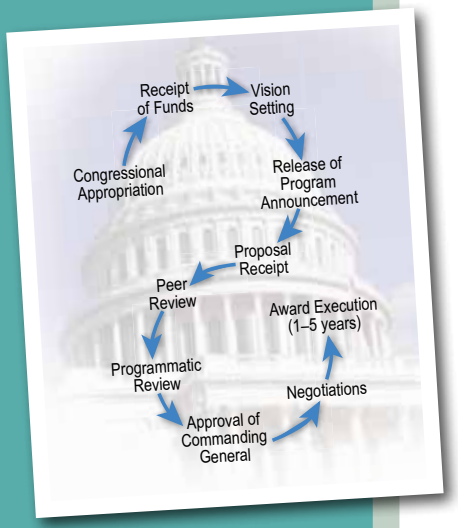
Ovarian Cancer Research Program





U.S. Army Medical Research and Materiel Command

Congressionally Directed Medical Research Programs



History of the CDMRP

The Office of the Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military. The CDMRP has grown to encompass multiple targeted programs and has received $7.061 billion in appropriations from its inception through fiscal year 2012 (FY12). 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.

Did you know?

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

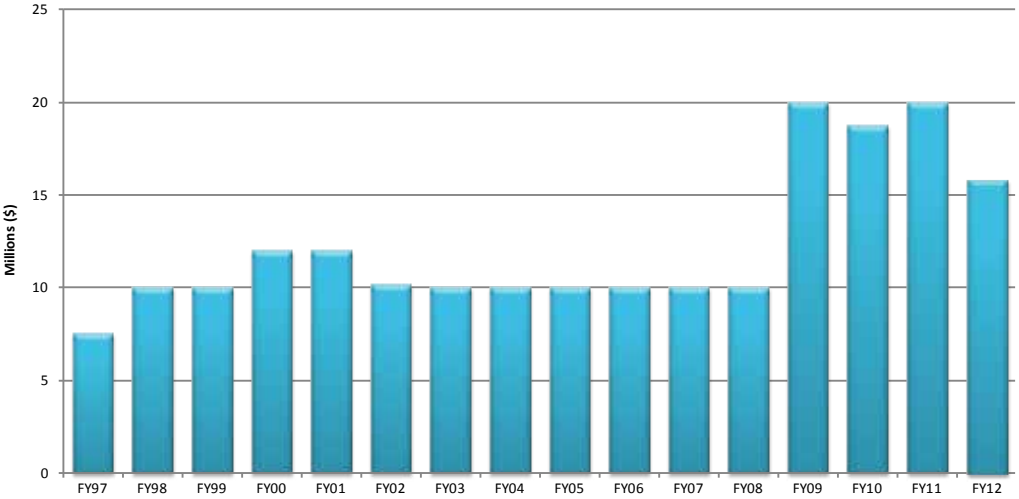
Dr. Patricia Kruk, Peer Reviewer, University of South Florida

"Being a reviewer on these DoD panels is really a unique experience. It is also very rewarding because not only as a scientific reviewer am I there to judge the scientific merit of a potential grant application, but it's also a constant reminder that we need to be innovative and we need to be focused and to have a product—end-product that could be clinically applicable. And this is always emphasized by the presence of consumer reviewers within the panel review. They put a real face to the disease and a reminder of what we are doing and why we are there."

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, impact, and relevance to program goals.

Congressional Appropriations for the OCRP FY97–FY12



Ovarian Cancer Research Program

History of the DoD OCRP

In FY97, the Congressional Appropriations Conference Committee Report No. 104-863 provided $7.5 million (M) to be administered by the DoD for ovarian cancer research. Since then, dedicated efforts by 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 $196M to the OCRP, including $16M in FY12. Each year the OCRP vision is adapted, and in response to dynamic changes in the field, an investment strategy is developed to ensure that funds are best directed toward the most critical needs and scientific gaps. The OCRP evaluates the funding landscape by comparing research portfolios and mechanisms of other federal and non-federal agencies and 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.

Key Initiatives of the DoD OCRP

- Leverage critical research resources
- Challenge current thinking and approaches
- Support high-impact, innovative research
- Accelerate movement of promising ideas into clinical applications
- Facilitate synergistic, multidisciplinary, and nontraditional collaborations
- Cultivate the next generation of ovarian cancer researchers

Did you know?

- **Since the inception of the DoD OCRP, more than 130 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!**

VISION

Eliminate ovarian cancer.

MISSION

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

Dr. Nicole Urban, Fred Hutchinson Cancer Research Center

"The focus on innovation and impact did start with the DoD, and I think it's one of the things that has made that program as successful as it has been. They're not just funding people based on track record and preliminary work; they're looking for some real commitment to making a difference in the disease—the impact part—and being innovative."

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 (also called consumer advocates), clinicians, and scientists brings together stakeholders that typically might not collaborate, and it has shaped the DoD OCRP as well as changed the way research is funded. Ovarian cancer consumers have played a pivotal role in the establishment and impact of the OCRP. Through this partnership, ovarian cancer consumer advocates work together with scientists and clinicians to identify research that will lead to the understanding, early detection, diagnosis, prevention, and management of ovarian cancer.

On a yearly basis, the OCRP's IP defines the program's vision and investment strategy. The voices of the ovarian cancer consumer advocates provide a different perspective and bring a sense of urgency and the human dimension of the disease into the DoD OCRP's policy, investment strategy, and research priorities. The two-tier review of research applications utilized by the OCRP brings together ovarian cancer survivors' firsthand perspectives with the expertise and knowledge of scientists and clinicians on the peer and programmatic review panels. While peer review provides expert advice on the technical merit of research applications, the OCRP IP makes funding recommendations that best meet the OCRP's program goals. The ovarian cancer survivor's perspective helps scientists and clinicians understand how the research will impact the ovarian cancer community, and moreover, it encourages funding of research that reflects the needs of patients and their families as well as the clinicians who treat them.

The OCRP has expanded the role of the ovarian cancer survivor through collaborative research in which the survivor is integrated into the project design, recruitment, and execution of the research.

Did you know?

- **Since 1997, consumer advocates have participated in setting the OCRP research priorities.**
- **Consumer advocates have participated as equal voting members during scientific review of research applications.**
- **Consumer advocates have participated as equal voting members in making funding recommendations during programmatic review.**
- **To date, more than 600 scientists, clinicians, and ovarian cancer consumer advocates have participated in the OCRP's two-tier review process of research projects.**

Dr. Patricia Donahoe, Academy Dean, Massachusetts General Hospital

"The DoD has brought leaders in the field of ovarian cancer together and said okay… What can we do differently? What mechanisms can they put in place?"

Serving as a consumer reviewer for OCRP has allowed me to feel that I am in some way contributing to the advancement of research that could result in earlier detection and eventually a cure for ovarian cancer. As a 7-year survivor of the disease, I personally dedicate the work I do in loving memory of the many I have met who did not survive and to those future women who will also have to make this cancer journey.

~Virginia Moore, The Wellness Center, Arizona

Ovarian cancer is a tricky disease. We have an urgent need for everything: an early detection tool, more effective treatments in first line and for recurrence, better imaging, and greater understanding of disease origination. The OCRP is focused on funding cutting-edge research in all these areas, and serving as a consumer reviewer is an exciting and rewarding experience. Reviewing each research proposal feels like opening a gift. I think to myself, "Is this it? Will this be the one to uncover a major breakthrough that will make a huge difference for women living with ovarian cancer?" The answers are out there and innovative researchers need the funds to find them. I feel lucky to be enjoying a very long third remission. The OCRP will bring us closer to the day when ovarian cancer survivors no longer have to rely on luck for a good outcome.

~Annie Ellis, Ovarian Cancer National Alliance, New York

As a 5-year ovarian cancer survivor and patient advocate representing the National Ovarian Cancer Coalition, I have had the privilege of serving on OCRP peer review panels since 2008. I am consistently impressed with the dedication and efficiency of the CDMRP staff in the coordination of this program and the commitment of the researchers serving on these committees. I applaud the CDMRP for introducing this unique funding mechanism that continues to play a crucial role in the development of early detection methods and research leading to more effective treatments. The depth of discoveries that has been credited to this funding mechanism is significant, and I always look forward to sharing the impact of these research programs with fellow survivors. OCRP panel peer reviewers have the common goal of identifying the most promising proposals that have the greatest potential of eradicating a disease that has cut short too many lives. I am optimistic that the time will come when we no longer have a need for these programs because we have completed our mission of finding a cure for ovarian cancer.

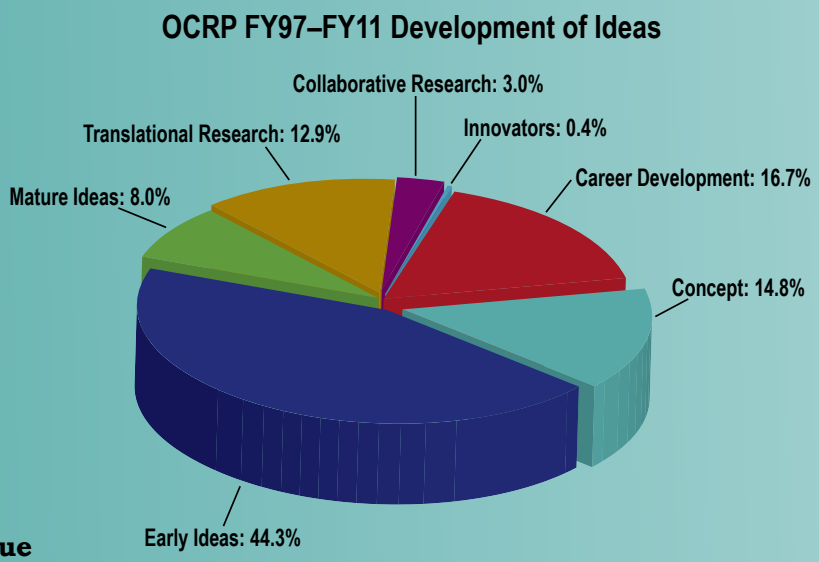
~Debbie Miller, National Ovarian Cancer Coalition, Texas

Did you know?

- **More than 230,000 women are diagnosed with ovarian cancer worldwide each year and about 140,000 women die from the disease.**

THE DoD OCRP TREK:

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



The DoD OCRP has been filling unique niches by encouraging and supporting high-impact research in areas that are unmet within the ovarian cancer community. The DoD OCRP has accomplished this by thinking differently, creating novel award mechanisms, focusing on critical needs, and supporting synergistic and nontraditional partnerships.

1997 Beginning of the DoD OCRP

» First DoD OCRP appropriation

» Ovarian cancer advocates launch grassroots campaign to increase research funding

1997–2001 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; animal models

» Established critical, synergistic partnerships in the International OCAC* and the AOCS**

1999, 2002–2012 Supporting Innovative Research

» Supported innovative, high-risk/high-reward research leading to critical discoveries driving the field forward

» Expanding or modifying current thinking and approaches in ovarian cancer

» Supported a visionary leader, the "Teal Innovator," to focus his creativity on paradigm-shifting ideas in ovarian cancer

1999–2000, 2005–2006 Bringing Talented Investigators into Ovarian Cancer Research

» Developed junior faculty and career transition independent researchers

» Supported HBCU/MI*** investigators in developing research resources and careers

**Ovarian Cancer Association Consortium*
***Australian Ovarian Cancer Study*
****Historically Black Colleges and Universities/Minority Institutions*

2007–2012 Translational 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 and to amplify potential gains in knowledge

2007–2012 Collaborations

» Supported partnerships between clinicians and laboratory scientists to transform ideas into clinical applications

» Created the Translational Leverage Award to leverage existing human-based ovarian cancer resources in translational research

2009, 2011–2012 Collaborative and Interactive Research Environment

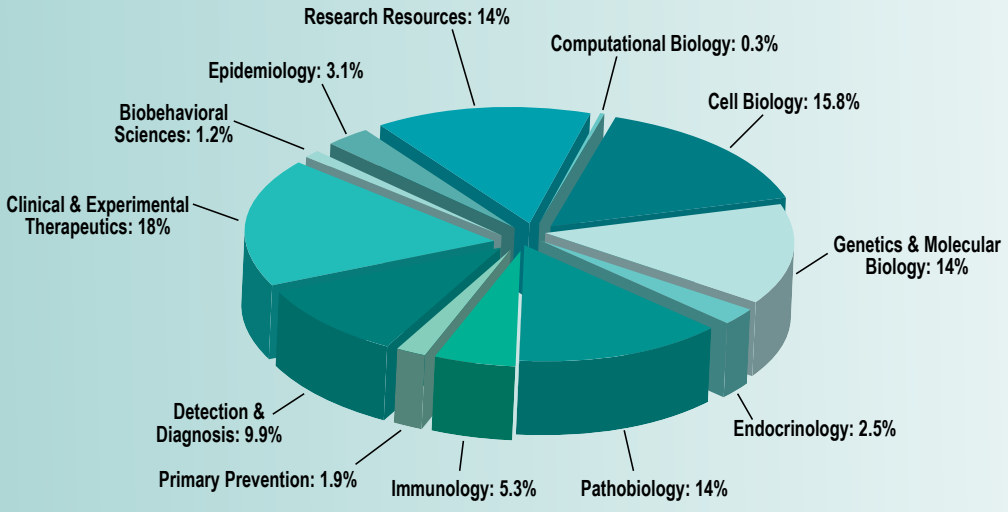
» Created the Ovarian Cancer Academy, an interactive, virtual mentoring and networking platform with 7 highly committed junior faculty, their mentors, and an Academy Dean

» Offered the first nested Teal Predoctoral Scholar option to foster the next ovarian cancer investigators through mentored research training

2011–2012 Leveraging Resources

» Created the Synergistic Translational Leverage and Translational Leverage Award mechanisms for leveraging existing human-based ovarian cancer resources for maximum use beyond the original source

OCRP FY97–FY11 Portfolio Categorized by Research Area



The DoD OCRP –

The DoD OCRP's overall goal is to eliminate ovarian cancer by supporting high-impact research and using multiple approaches to target research gaps in ovarian cancer. Over the program's history, the OCRP has focused on:

Leveraging Existing Resources

Dr. Karin Rodland, IP Member, Pacific Northwest National Laboratory

"Leveraging is important for the Ovarian Cancer Research Program because resources are tight, and it's very important to get the most benefit out of what we're doing."

The OCRP focuses on leveraging existing human-based ovarian cancer resources to eliminate duplication of research resources. Many ovarian cancer resources are confined to investigators' labs where they were first developed and are not always leveraged for maximum use beyond the original source. Some human-based resources are expensive to generate, maintain, and make available to other investigators, but they may have broad applicability across many different types of research questions. The OCRP leverages critical research resources through its Translational Leverage and Synergistic Translational Leverage Award mechanisms, which require that existing human-based resources be used in the research project and then the results or outcomes be made available for use by others.

Translation of Science to the Clinic

Critical components in the research continuum are mechanisms to carry out the translation of promising strategies for prevention, detection, diagnosis, and treatment to clinical trials. Translational research spans the continuum from discovery of a target to clinical trials. The OCRP supports translational research through a variety of mechanisms.

- The Translational Pilot Award mechanism supported early-stage translational research ideas through preclinical studies; these ideas are expected to challenge or expand current thinking or approaches to ovarian cancer.
- The Translational Research Partnership award funds correlative studies associated with a clinical trial while the Translational Leverage Award supports translational research along the entire continuum including clinical validation studies.

Facilitating Collaborative Partnerships

Recognizing that research collaborations are important in investigating the increasing complexity of disease, the OCRP has developed "Team Science" award mechanisms that bring together the most talented scientists from different disciplines and different 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 and can unravel complex phenomena and significantly accelerate progress.

- The OCRP Translational Research Partnership Award mechanism requires a collaboration in which one partner must be a laboratory scientist and the other must be a clinician to help move an observation from the lab into clinical application.
- The key initiative of the Collaborative Translational Research Award was to establish multi-institutional, multidisciplinary collaborations among clinicians and laboratory scientists conducting translational research.
- To promote building multi-institutional collaborations into consortia, the OCRP offers Consortium Development and Consortium Award mechanisms.

Complementary Approaches to Eliminating Ovarian Cancer

Encouraging Visionary Individuals

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

Cultivating Ovarian Cancer Researchers

Building a critical mass of dedicated, career ovarian cancer researchers is essential to eliminating ovarian cancer. The OCRP 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. A nested Teal Predoctoral Scholar is offered as an optional feature of the Pilot and Translational Pilot Award mechanisms to train graduate students in both basic and clinical ovarian cancer through mentored research training.

Fostering Innovative, High-Impact Research

The OCRP Pilot Award supports 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 potentially, in the future, reduce the burden of this disease.

FY12 OCRP – Accelerating Promising Ideas

The FY12 OCRP continues to focus on innovative, high-risk/high-reward research that may lead to critical discoveries or major advancements through the Pilot Award. While this award accepts projects from all areas of ovarian cancer research, the FY12 OCRP encourages research from the following areas: using novel approaches for improving the performance and validity of predictive disease markers; understanding the mechanistic basis of disease markers; generating novel imaging/molecular imaging approaches for screening and management; generating innovative insights in etiology, risk factors, and outcomes for ovarian cancer; and identifying and validating molecular targets for therapy.

In addition, the Ovarian Cancer Academy Award will add new early-career investigators to the virtual academy that provides an interactive, collaborative research training platform. FY12 will also see the return of the Teal Innovator Award, a mechanism that provides a visionary individual with the resources to create paradigm-shifting ideas to accelerate progress toward the elimination of ovarian cancer.

New for FY12 are the Synergistic Translational Leverage and Outcomes Consortium Development Award mechanisms. The Synergistic Translational Leverage mechanism supports the partnership between two investigators who will leverage existing human-based resources to address high-impact research in ovarian cancer. The Outcomes Consortium Development mechanism, the first phase in a two-phase mechanism, facilitates the development of a consortium that will specifically focus on identifying and understanding predictors of disease outcomes in ovarian cancer patients. Importantly, the Outcomes Consortium Development mechanism integrates ovarian cancer survivor advocates as partners with the scientists and clinicians on these research teams, with the survivor advocates adding a perspective and a sense of urgency that only they can provide.

Teal Innovator for OCRP 2011
A Researcher's Perspective

Dr. Garry Nolan, Stanford University

For most cancers it is already established that they are "heterogeneous." Thought of another way, cancer cells are like a puzzle that has been so jumbled and distorted that it is impossible to put the pieces back together again. Further definition of a given tumor's subtype is generally not done because scientists have not had a technique to classify important features of millions of cancer cells at a time in a manner that would allow us to piece together a puzzle.

Despite the confusion of markers, cell types, and genetics associated with ovarian cancer, it is my strong belief that there exist underlying "currents" of biology and pathology across tumors. By dissecting cancer into its many components and studying those components simultaneously and at the deepest possible single-cell resolution available, I believe we can provide a unifying vision of ovarian cancer "systems biology" to enact real and long-term changes in our understanding of this disease as well as bring about changes to treatment modalities. Understanding how every single cell in a tumor can or cannot respond to drug action and the manners by which ovarian cancer resists current cancer treatment (by our group's unique ability to interrogate on a cell-by-cell basis all known steps in the pathway from initiation to apoptosis) will provide the cancer community a resource of unprecedented utility.

Clearly, a more accurate and reliable means of classifying the cells in tumors such as ovarian cancer is required. Recently my laboratory has been focused on validating a new adaptation of flow cytometry called mass cytometry to study complex samples, such as human tumors, at the single cell level. The technique, published in *Science* last year, allows us to tag key "sentinel" proteins that cancer changes as they divide. One can think of this process of cancer growth as a slow, but repeating, morphing effect. After multiple cell divisions, some cancer cells no longer look like their great-great grandparent cells. Our technique allows us to trace the lineages and reconstruct the family tree of ovarian cancers.

By applying mass cytometry to 40 primary ovarian cancer samples, we found that even across different patients a common family tree is formed. But each patient populates the tree to varying extents. Each patient when looked at in isolation appears different, but when the patients are "mapped" together, it can be seen that they form common trees. We will now extend our studies to many more samples and delve into which cells are the best to target. So our original hypothesis was confirmed—cancers are not infinitely varying. More importantly, this allows us to define a common lineage tree for the ovarian cancer cells across all samples in our cohort. Our priority is to determine whether there are different responses of each branch to important clinical drugs. Given that we find that to be true in other cancers, the likelihood of different responses between "branches" of cells in an ovarian cancer sample is highly likely.

While cancer is both a clinical and societal problem of huge importance, my Teal collaborator, Dr. Wendy Fantl, and I are currently cancer survivors from kidney cancer, melanoma, and early-stage ovarian. Nothing could be more motivating than studying a disease where personal involvement is so real. My laboratory and those of our collaborators are firmly committed to a large-scale effort in this malignancy.

My focus over the past decade has been as a recognized leader in the development and application of new technologies for which I have led multiple initiatives with cross-disciplinary teams. Specifically, I have been using our ovarian cancer data as a leading-edge model of a new way to think about cancers in general. Basically, our message is that cancers can be organized, can be mapped, and we can finally understand which cells a given drug has activity against and map this to the molecular biology of the disease.

We hope that our work can overcome one or both of the major barriers (deeper classification and early detection) to improving therapeutic outcome for ovarian cancer patients. We expect that deep proteomic profiling of single cells enabled by single-cell mass cytometry will have the greatest impact in providing a far more detailed characterization of the disease with potentially major implications for choosing the optimal therapeutic outcome of those existing or providing a lead for development of new targeted agents. Additionally, it is quite likely that a byproduct of our research could lead to new approaches for early detection.

Did you know?

- **One in 70 women will develop ovarian cancer in her lifetime.**
- **Ovarian cancer causes more deaths than any other cancer of the female reproductive system.**
- **There is no early detection test for ovarian cancer. A Pap smear will NOT detect it.**

High-Impact Research That Is Moving the Field Forward

OCRP researchers are taking unique approaches to gain a deeper understanding of ovarian cancer that will ultimately benefit women affected by the disease. They are working toward the development of minimally invasive tests for early detection and diagnosis, employing innovative approaches to understanding risk factors of ovarian cancer and potential methods for prevention, as well as conducting groundbreaking research into treatments for primary and recurrent disease. Their efforts are accelerating promising ideas toward clinical applications and contributing to the ultimate goal of eliminating ovarian cancer.

Did you know?

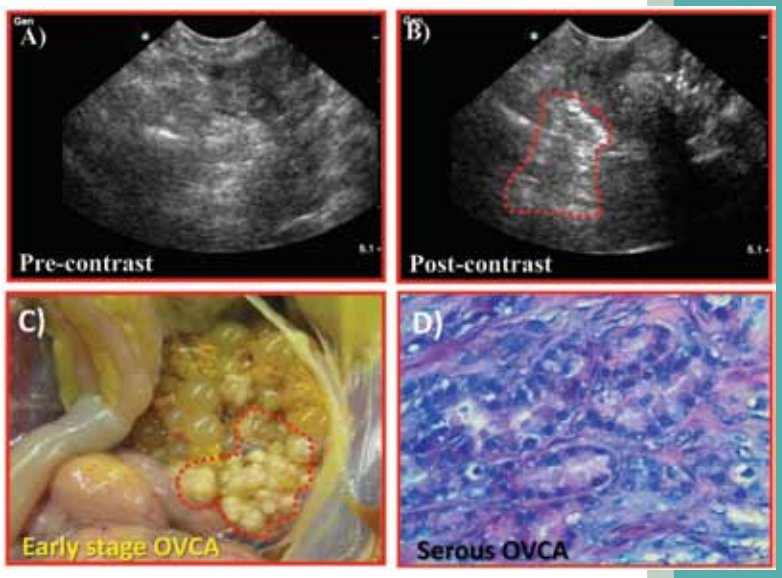
- **Lynch syndrome, which is hereditary nonpolyposis colon cancer, is associated with an increased risk of developing ovarian cancer.**

Early Detection of Ovarian Cancer by Contrast-Enhanced Ultrasound-Targeted Imaging

Dr. Animesh Barua, Rush University Medical Center

Only 15% of ovarian cancer cases are detected at an earlier, localized stage—most cases are detected at a later stage. There is still no early detection test for the disease. Transvaginal ultrasound can be used to detect ovarian cancer, but it is limited for early-stage disease. Dr. Barua's long-term goal is to improve the detectability of early-stage ovarian cancer by using molecular-targeted, contrast-enhanced ultrasound. Dr. Barua is focusing on changes in nuclear matrix proteins (NMPs) and ovarian tumor-associated neo-angiogenesis associated with early ovarian cancer development. Two biomarkers, αvβ3-integrins and death receptor (DR)-6, characterize the tumor-associated neo-angiogenesis while serum anti-NMP antibodies indicate early malignant changes in the ovary. The αvβ3-integrins will be used as molecular targets for contrast-enhanced ultrasound imaging in combination with anti-NMP antibodies and serum levels of DR-6. This research is being conducted with the egg laying hen model of spontaneous ovarian cancer.

Thus far, Dr. Barua has shown that targeting ovarian αvβ3-integrins with contrast-enhanced molecular ultrasound is capable of detecting neo-angiogenesis at early stages of the disease in the egg laying hen model. Additionally, he observed that serum levels of DR-6 were elevated in hens with early-stage ovarian cancer. Related research on anti-NMP antibodies and early ovarian tumor formation is ongoing.



Early detection of ovarian tumors by avβ3-integrins targeted contrast-enhanced ultrasound imaging. Compared to pre-contrast imaging (A), avβ3-integrins targeted contrast agent enhanced the visualization of the tumor remarkably (B). Ultrasound detection was confirmed at necropsy (C) and histology (D) showing the tumor was limited to a part of the ovary. The red dotted line indicates the solid mass in the ovary.

Dr. Barua was also recently awarded a Translational Pilot Award as well as a Pilot Award to continue studying early detection of ovarian cancer by using innovative molecular-targeted ultrasound imaging techniques. His research has the potential to significantly impact the early detection of ovarian cancer.

An International Consortium to Investigate Early Changes Associated with Ovarian Cancer Predisposition and Development

Back row left to right: Charles Drescher, Fred Hutchinson Cancer Center (USA); Martin Widschwendter, University College London (UK); Usha Menon, University College London (UK); Jessica Mcalpine, University of British Columbia (Canada); Santo Nicosia, University of South Florida (USA); Georgia Trench, Queensland Institute of Medical Research (Australia); Paul Pharoah, University of Cambridge (UK); James Brenton, University of Cambridge (UK); Peter Laird, University of Southern California (USA)

Front row left to right: Jeff Marks, Duke University (USA); Patricia Kruk, University of South Florida (USA); Louis Dubeau, University of Southern California (USA); Anna DeFazio, Westmead Millenium Institute (Australia); David Huntsman, University of British Columbia (Canada)

Dr. Louis Dubeau, University of Southern California

The goal of the Consortium Development Awards (CDAs) offered in FY08 and FY09 was to promote major multi-institutional research efforts that specifically focus on identifying and characterizing early pathologic changes associated with ovarian cancer. This mechanism was designed to provide funding for the development of the administrative infrastructure necessary to carry out successful multicenter collaborative research projects. Dr. Dubeau received an FY08 CDA to build a consortium to investigate the role of extra-uterine mullerian epithelium in ovarian cancer tumorigenesis. The Extra-Uterine Mullerian Epithelium Role in Tumorigenesis (EUMERIT) consortium specifically seeks to understand how the menstrual cycle and BRCA1/2 mutations influence genomic and epigenomic regulation of extra-uterine mullerian epithelium. Dr. Dubeau's team at the University of Southern California is joined by researchers at Duke University, New York University, The Moffitt Cancer Care Center, University College London (UK), Cambridge University (UK), Queensland Institute of Medical Research (Australia), and the University of Sydney (Australia) in this international consortium.

A mini-symposium was held in June 2009 for the members of the consortium to exchange scientific ideas, discuss the specific projects that EUMERIT will pursue, and begin to standardize research and sample collection protocols. In addition, the Fred Hutchinson Cancer Center and Mount Sinai School of Medicine, both in New York City, joined the consortium. Moving forward Dr. Dubeau plans to apply for additional funding to support the EUMERIT consortium, including a Program Project Award from the National Institutes of Health.

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

Dr. Robert Kurman, Johns Hopkins University, Consortium Award

In 2010, Dr. Kurman of Johns Hopkins University and his group were awarded the first Ovarian Cancer Consortium Award. With a focus on identifying and characterizing early changes of disease associated with ovarian cancer, this research has the potential to significantly impact ovarian cancer incidence and mortality. Dr. Kurman and his collaborators from four research sites will test the overarching hypothesis that a lesion in the fallopian tube (and fimbria) called a serous tubal intraepithelial carcinoma (STIC) is the precursor of many, if not most, ovarian high-grade serous carcinomas (HGSCs); however, they will also investigate the other proposed candidates (ovarian surface epithelium and ovarian cortical inclusion cysts). HGSC is of particular importance because it accounts for 75% of all ovarian cancers and 90% of deaths.

The consortium's four preclinical projects and the epidemiology project are in progress. These projects will determine whether STICs are the precursor lesions of primary HGSC, assess all proposed sites of origin, identify early molecular changes that precede STIC development in addition to establishing molecular and epidemiological profiles of putative precursor lesions in the ovaries and fallopian tubes of women at high risk for ovarian cancer. Consortium researchers will also locate and characterize precursor lesions in an ovarian cancer mouse model and study the role of ovulation and changes in the microenvironment of the ovary and fallopian tube during ovarian carcinogenesis. To date, the consortium's pathologists have developed and validated an algorithm for the diagnosis of STICs. This algorithm is available on the website that was established for researchers and patients (http://www.ovariancancerprevention.org/). Dr. Kurman and his associates have also identified a potentially useful tissue biomarker, LAMC1 encoding laminin, a gene that is overexpressed in HGSC. This discovery will help researchers diagnose STICs and will contribute to a better understanding of the early events associated with this disease.

Did you know?

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

Early Detection of Epithelial Ovarian Cancer Using Exhaled Breath Markers: GC/FT-ICR Mass Spectrometry and Canine Olfaction

Dr. Touradj Solouki, Baylor University

Early detection of ovarian cancer is critical for obtaining the best possible outcome but to date no reliable test exists. Dr. Solouki was awarded an Idea Development Award in 2006 for work differentiating the exhaled breath of women with ovarian cancer from controls. One of the projects in this award involved comparing the condensed exhaled breath of women with ovarian cancer from those without using a highly sensitive gas chemical analyzer (a gas chromatography Fourier transform ion cyclotron resonance mass spectrometer) to measure their contents. The ultimate goal of this work is to develop a reliable set of markers for ovarian cancer that can be measured noninvasively from condensed breath. During this award, Dr. Solouki developed a new technique for identifying and measuring a broad scope of proteins using the previously described mass spectrometer. A patent application is under way for this methodology, and future applications include improved detection of trace molecules in condensed breath or saliva. Dr. Solouki also wrote a specialized computer program to aid in analyzing the large amounts of data that are generated by the highly sensitive spectral analysis, which will speed future analyses using this tool.

Early Detection of Ovarian Cancer

Dr. Martin McIntosh, Fred Hutchinson Cancer Research Center

Early detection of ovarian cancer continues to be a difficult hurdle in treating this disease; to date no reliable test exists as there is still much to learn. In 2005, a team at Fred Hutchinson Cancer Research Center led by Dr. McIntosh was awarded an Idea Development Award to pursue work in identifying meaningful biomarkers derived from normal proteins that are altered by ovarian cancer. Dr. McIntosh used two methods of detection: first a library of lab-made antibodies tested on patient samples and then a mechanical chemical detection method called tandem mass spectrometry (a multistep process of measuring the charge and weight of molecule fragments to identify compounds). These methods were tested on a set of samples that are advantageous for early discovery, including serum samples from before clinical diagnosis. Using these techniques, Dr. McIntosh and his team were able to identify a number of potentially useful markers that are undergoing further study. Dr. McIntosh was recently awarded a Teal Expansion Award in 2011 to continue his work seeking even more sensitive ways to identify proteins that are altered by cancer by sequencing coding RNAs. He will then evaluate their use in diagnosis and also in therapy and prevention.

Did you know?

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

University of South Florida Ovarian Epithelium Cancer Pathobiology Program Investigators

In FY01 Dr. Santo Nicosia was awarded OCRP Program Project funding with Drs. Jin Cheng and Patricia Kruk, both recipients of FY99 New Investigator Awards, serving as project leaders to investigate cell growth and survival in epithelial ovarian cancer (EOC). Since then, these investigators have continued their research to identify biomarkers and novel therapeutic targets for ovarian cancer.

Dr. Santo Nicosia

During the Program Project Award, Drs. Nicosia and Cheng began to elucidate the mechanism by which ascorbyl stearate, a source of vitamin C, induces apoptosis of ovarian cancer cells. These clinically important results provide the basis for future investigations into a nontoxic, complementary therapy for ovarian cancer. Dr. Nicosia received funding from an FY09 Idea Development Award to evaluate angiotensin, which stimulates the growth of blood vessels in tumors and normal tissues, as a potential biomarker for ovarian cancer. His work revealed that levels of angiotensin were elevated in urine samples from women with EOC compared to samples from healthy controls and women with benign gynecological disorders.

Dr. Jin Cheng

Dr. Cheng's work during the Program Project Award demonstrated the AKT2, which is elevated in about 40% of ovarian tumors, contributes to chemoresistance by regulating molecules in the apoptotic pathway. Additionally, he demonstrated that the AKT inhibitor triciribine had strong potential as a treatment for ovarian cancer, leading to a Phase I clinical trial. The Phase I trial has been completed and is moving forward to Phase II.

With funding from an FY04 Idea Development Award, Dr. Cheng established a role for the oncogene Aurora-A in ovarian cancer chemoresistance. This finding identified Aurora-A as both a biomarker and potential therapeutic target for ovarian cancer. In FY07 Dr. Cheng was the recipient of a Concept Award to identify microRNAs, small RNA sequences that negatively regulate gene expression, involved in ovarian cancer chemoresistance. Two microRNAs were demonstrated to be involved in chemoresistance in ovarian cancer cells and were associated with a poor clinical prognosis. Dr. Cheng also found that knockdown of a third microRNA in ovarian tumor cells led to increased cell death. Dr. Cheng is building upon these findings with funding from an FY10 Translational Pilot Award to characterize inhibitors of these microRNAs, which could become therapeutic targets for ovarian cancer.

Dr. Patricia Kruk

Dr. Kruk's study during the Program Project Award confirmed that activation of the cellular enzyme telomerase reduced apoptosis of ovarian cancer cells. She also demonstrated that vitamin E suppressed telomerase activity in ovarian cancer cells and enhanced cisplatin-mediated cell death, supporting a protective role for vitamin E against ovarian cancer growth. In FY06, Dr. Kruk received an Idea Development Award to determine whether Bcl-2 could be used as a biomarker for ovarian cancer. Analysis of Bcl-2 levels in urine samples showed that urinary levels were elevated in ovarian cancer patients, regardless of tumor grade, stage, size, and subtype. If these findings are validated by other investigators, Bcl-2 detection in urine could provide a noninvasive, low-cost method to detect ovarian cancer. This work represents an important step in translating laboratory findings into clinical applications.

Dr. Mary Daly, Fox Chase Cancer Center

"One of the things that makes the DoD grants innovative is that they particularly look for collaborations. The DoD grants began a new model of almost requiring that people from different disciplines work together to solve the ovarian cancer problem."

Wnt Signaling, Cellular Senescence, and Epithelial Ovarian Cancer Therapy

Dr. Rugang Zhang, Wistar Institute

Dr. Zhang is investigating a means to stop ovarian cancer by triggering a phenomenon called cellular senescence (or cellular aging)—the process whereby normal cells in the body stop dividing and enter a state of irreversible silence. This process essentially prevents cells from growing without killing them. Ultimately, the goal of his study is to utilize this natural cell behavior as part of a novel therapeutic strategy to combat ovarian cancer.

Toward this goal, Dr. Zhang is exploring how the so-called Wnt signaling pathway—a network of chemical signals within cells—is activated by the loss of a protein called Wnt5a. Without Wnt5a, EOC can bypass the natural senescence process, thereby allowing these ovarian tumors to thrive unchecked. He has found that Wnt5a is produced at lower levels in ovarian cancers, and the loss of Wnt5a leads to rapid cell division (a hallmark of cancerous growth). In addition, Wnt5a loss is noted as a biomarker for poor prognosis in EOC.

Dr. Zhang observed that functioning Wnt5a suppressed the growth of human ovarian cancer cells in both cell culture and mouse models of the disease. Moreover, he found that reconstituting Wnt5a in ovarian cancer cells caused the cells to senesce. Based on his results, he concluded that targeting Wnt signaling is a novel strategy for causing EOC cells to undergo senescence, which may form the basis of a therapeutic means to treat this disease.

Dr. Rugang Zhang, Academy Member, Wistar Institute

"As a young investigator I benefitted enormously from the DoD OCRP Ovarian Program, I was trained as a molecular and cellular biologist. It is through this program that…I truly transformed into an ovarian cancer researcher."

Targeting a Novel and Critical Vasculogenesis Pathway in Ovarian Cancer

Dr. George Coukos, University of Pennsylvania, Philadelphia

Tumor growth is often supported by the formation of new blood vessels to "feed" the tumor. Dr. Coukos was granted an Idea Development Award in 2005 to evaluate a set of candidate proteins for specific expression in tumor blood vessels. Work supported by this award led to the identification of nine such markers that have potential use as therapy targets or imaging targets. A patent application was filed covering this set of markers. Dr. Coukos is now pursuing additional research in targeting these proteins in an effort to develop more personalized medicine. He is conducting preclinical and Phase I testing on a potential cancer patient vaccine therapy to enhance the immune response against ovarian cancer. This type of treatment would take a woman's own immune cells and prime them to increase their response to the panel of identified cancer vasculature-specific proteins. He also tested a specialized antibody against the protein tumor endothelial marker 1 (TEM1) and confirmed in a mouse model that this is a valid individual candidate for targeting cells in tumor blood vessels. Together, this work has increased the number of potentially individualized therapeutics in the pipeline for ovarian cancer and continued the translation of lab findings to potential patient treatment.

Integrated Computational Biology Approach to Marker Selection for Early Detection and Treatment of Epithelial Ovarian Cancer

Dr. Igor Jurisica, University Health Network, Toronto, Ontario

Researchers need a better understanding of ovarian cancer subtypes to reliably identify and target these women for treatment in the future. Dr. Jurisica, at the Ontario Cancer Institute, part of the University Health Network in Toronto, was awarded a New Investigator Award in 2004 for his work expanding the definition of cancer subtypes. He created several related portals for such analyses, namely expanded the physical protein-protein interaction database (I2D; http://ophid.utoronto.ca/i2d) to enable network analysis of signatures and biomarkers, and created a Cancer Data Integration Portal (http://ophid.utoronto.ca/cdip), a publicly available resource that analyzes the datasets from

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

"We kind of have a standard of care in terms of treatment, but we don't know who it's going to work for."

published articles and available databases for differences in gene and protein expression, to better cover the ovarian cancer field. He developed a companion program NAViGaTOR (Network Analysis, Visualization, and Graphing Toronto; http://ophid.utoronto.ca/navigator) to help visualize and analyze these interactions and deregulated cancer networks. These tools are now used by Dr. Jurisica's lab and other scientists. The ability to mine available datasets gives researchers greater power than they can obtain by collecting the samples independently and, therefore, is more likely to speed up the research on this disease.

Dr. Jurisica also evaluated protein expression from fallopian epithelial cells in women with BRCA1 mutations, either with or without neoplasia or HGSC. Initial analyses that identified markers of high- or low-grade ovarian cancer, poor or good outcome, and neoadjuvant or adjuvant samples were confirmed. Computer-guided analyses also identified a number of ovarian cancer-related kinases. These findings will help guide the ovarian cancer research field going forward, as the identification of markers can help scientists accurately categorize particular subsets of women who benefit from a given treatment and, in turn, inform the research generating new therapies.

To further research in this direction, Dr. Jurisica's lab created several additional publicly available resources, such as SCRIPDB (http://dcv.uhnres.utoronto.ca/SCRIPDB/search/), which is a database of more than 11 million compounds extracted from U.S. patents, and NetwoRx (http://ophid.utoronto.ca/networx) containing a collection of chemogenomics screens that enable drug:pathway and drug:gene analyses and drug repurposing. Following these analyses, Dr. Jurisica and Dr. Amit Oza were awarded a Translational Leverage Award in 2011 to link prognostic signatures with new treatment options for patients.

(L-R) Professor David Bowtell, Ms. Kathryn Alsop and Dr. Gillian Mitchell, Familial Cancer Centre (GM) and Cancer Research Division

Genetic Profiling in the Australian Ovarian Cancer Study

Drs. Gillian Mitchell and David Bowtell, Peter MacCallum Cancer Centre

One of the most well-defined risk factors for ovarian cancer is an inherited germline mutation in either the BRCA1 or BRCA2 genes. It is therefore important to characterize the clinical, pathological, family history, and molecular factors that can predict BRCA1/2 mutations and understand the effect of BRCA1/2 mutations on ovarian cancer treatment outcomes. Drs. Gillian Mitchell and David Bowtell, recipients of an FY07 Translational Research Partnership Award, sought to evaluate the frequency and impact of germline BRCA1/2 mutations in 1,001 population-based ovarian cancer cases. The research was led by Ph.D. student Ms. Kathryn Alsop and leveraged existing samples and case information from the Australian Ovarian Cancer Study (AOCS), funded by the DoD OCRP in 2000. BRCA1/2 mutations were identified in 14% of the 1,001 samples from women with invasive nonmucinous ovarian tumors, similar to that reported previously by Canadian researchers. Importantly, AOCS researchers found that BRCA1/2 germline mutations were predominantly restricted to high-grade serous cancers where the combined frequency was 22.7%. Almost half of the women carrying BRCA1/2 mutations did not have a significant family history of breast or ovarian cancer. These findings challenge the current practice of offering genetic testing only to women with a positive family history of breast or ovarian cancer.

Very detailed clinical information was associated with the AOCS samples, allowing researchers to compare responses to first and second lines of chemotherapy in carriers and noncarriers. Enhanced responses to platinum and nonplatinum-based chemotherapy were seen in mutation carriers in both first- and second-line treatments. The researchers' findings have important implications for use of conventional chemotherapy in mutation carriers and the design of clinical trials in women with high-grade serous cancer.

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).**

The Ovarian Cancer Academy in 2012

The Ovarian Cancer Academy, a virtual career development and research training platform, convened for its first inaugural meeting on May 9, 2012. These highly committed early-career investigators, their mentors, and the Academy Dean have been busy collaborating and networking as they work toward eliminating ovarian cancer and becoming the next generation of leaders in ovarian cancer research. Cumulatively, they have published more than 65 ovarian cancer research articles, presented at national conferences, filed patents, mentored trainees, and served on editorial boards as well as peer review panels. The DoD OCRP is proud of their accomplishments as they continue to make strides in their fields.

Back row left to right: Anda Vlad, Magee-Women's Hospital; Rugang Zhang, Wistar Institute; Martina Bazzaro, University of Minnesota; Jeremy Chien, University of Kansas; Panagiotis Konstantinopoulos, Beth Israel Deaconess Medical Center; Kathryn Terry, Brigham and Women's Hospital; Charles Landen, University of Alabama, Birmingham

Front row left to right: Amy Skubutz, University of Minnesota; Michael Seiden, Fox Chase Cancer Center; Patricia Donahoe, Massachusetts General Hospital; Daniel Cramer, Brigham and Women's Hospital; Ronald Alverez, University of Alabama, Birmingham

Dr. Martina Bazzaro, University of Minnesota

Dr. Bazzaro is targeting ubiquitin-mediated protein degradation pathways for ovarian cancer treatment. She is focused on diagnostic and prognostic markers, targeted therapy, and the inhibitors' potential mechanisms of anti-cancer activity. Dr. Bazzaro has found de-ubiquitinating enzymes (DUBs) involved in ovarian cancer cells, and she is testing probes to specifically target those DUBs and cells that overexpress them. Targeting the DUBs may lead to a new treatment for ovarian cancer in the future.

Dr. Jeremy Chien, University of Kansas

Dr. Chien is investigating integrative functional genomics and proteomics to uncover mechanisms of chemotherapy resistance in ovarian cancer. Using the TCGA (The Cancer Genome Atlas) data, he has found a list of genes that could be used to predict diagnosis of ovarian cancer. Dr. Chien observed a difference between tumors that express high and low levels of the gene FBN1, and while it may have no role in primary resistance, it may have a role in delayed resistance or platinum-sensitive recurrence. He also proposed a new model of chemotherapy resistance that builds on other existing models. Results from Dr. Chien's work may be able to help improve patients' responses to chemotherapy.

Dr. Panagiotis Konstantinopoulos, Harvard Medical School

Dr. Konstantinopoulos is working toward developing a biomarker for "BRCAness," a phenotype that is characterized by responsiveness to platinum and PARP (poly ADP ribose polymerase) inhibitors and improved survival in patients. He is investigating the association of the BRCAness gene expression profile with clinical outcome and molecular aberrations underlying defective homologous recombination in high-grade, advanced stage EOCs in the TCGA dataset. Dr. Konstantinopoulos found that the BRCAness profile is associated with certain defects (e.g., events involving BRCA 1/2 genes and deletions of homozygous PTEN) in homologous recombination DNA repair. Additionally, he found that patients with BRCA-like tumors had improved overall survival when compared to patients with non-BRCA-like tumors. Efforts are under way to improve the predictiveness of the BRCAness profile.

Dr. Michael Seiden, FY12 IP Chair, Fox Chase Cancer Center

"The amount of science that needs to be covered to really get a global understanding of ovarian cancer is massive…So it does bring both special opportunities for researchers because there's a lot of room to make a difference, but it also requires… the ovarian cancer community to work hard to recruit young scientists, young clinical researchers into the field because we need more individuals to commit their time, energy, and talent to the problem."

"We want the best and the brightest young people to be working in ovarian cancer. We're kind of selfish that way. We want them in ovarian cancer. And you have to replenish the pipeline of bright, talented, trained investigators. You do that by giving them an opportunity to shine and an opportunity to do the research that interests them and guiding them in the direction of having that be ovarian cancer."

Dr. Karin Rodland, IP Member, Pacific Northwest National Laboratory

Dr. Charles Landen, University of Alabama at Birmingham

Dr. Landen is looking at the emerging aspect of cancer stem cells (i.e., tumor-initiating cells). His research is supportive of the hypothesis that subpopulations within heterogeneous ovarian tumors contribute to chemoresistance. Dr. Landen has shown that markers in ovarian cancer cells, "side population," CD44, CD133, and aldehyde dehydrogenase (ALDH1), have cancer stem cell-like properties. Additionally, results from an analysis of primary and recurrent tumors showed chemoresistant tumors were enriched in CD133 and ALDH1-positive cells although they were not the only ones in the chemoresistant population. His findings could contribute important targets for chemotherapy and overcoming chemoresistance in addition to helping build better models to understand tumor heterogeneity.

Dr. Kathryn Terry, Harvard Medical School

Dr. Terry's research is focused on understanding risk factors by etiologic pathway. Based on measurements from pathology reports, she and her colleagues have classified more than 1,700 cases from the New England Case Control Study and the Nurses' Health Study into dominant tumors (likely of ovarian origin) defined as those restricted to one side or with one side that is two times greater than the other and nondominant (likely tubal origin). They have found that dominant tumors are more strongly associated with multiparity, tubal ligation, and endometriosis, whereas nondominant tumors are more strongly associated with a family history of ovarian cancer and genetic variation in a telomere-associated protein, TERT. Results from Dr. Terry's work provide a better understanding of ovarian cancer risk factors, which is important for prevention.

Dr. Anda Vlad, University of Pittsburgh School of Medicine and Magee-Womens Research Institute

Dr. Vlad is working on preclinical modeling of ovarian cancer for vaccine development—she is using genetically engineered mice with conditional mutations in the Kras and/or Pten pathways for the preclinical modeling of gynecologic malignancies. She is focusing on the well-defined tumor antigen, MUC1, as an oncoprotein/vaccine candidate because it is overexpressed in more than 80% of EOCs. Dr. Vlad has found that MUC1 expression in her transgenic mice mirrors human MUC1 tissue distribution. She is testing MUC1 as a vaccine candidate in the transgenic mice and demonstrated that the vaccine significantly prolonged survival in vaccinated mice with ovarian tumors as well as restored immune surveillance. Additional results from her research indicate that MUC1 influences ovarian cancer pathogenesis and will be a valuable target for immune therapy.

Dr. Rugang Zhang, Wistar Institute

Dr. Zhang is exploring how canonical Wnt signaling activated by loss of Wnt5a contributes to EOC development through overcoming senescence, a state of irreversible cell growth arrest. He has found that Wnt5a is expressed at lower levels in primary EOCs, and the loss of Wnt5a correlates with a high cell proliferation index. It was a poor prognosis biomarker in EOC as well. Dr. Zhang observed that Wnt5a suppressed the human EOC cell growth in vitro and in an orthotopic mouse model. Reconstituting Wnt5a induced senescence in EOC cells too. Based on his results, he concluded that targeting Wnt signaling is a novel strategy for causing EOC cells to undergo senescence, which may be a possible mechanism for ovarian cancer therapeutics.

Did you know?

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

OCRP Nested Teal Predoctoral Scholars

In FY09, the OCRP offered a nested Teal Predoctoral Scholar option in the Idea Development Award. The intent of the nested Teal Predoctoral Scholar is to foster the next generation of ovarian cancer investigators through mentored research training of doctoral degree candidates who are committed to a career in ovarian cancer. In FY10–FY11, the Teal Predoctoral Scholar option was offered again with the Pilot and Translational Pilot Awards. These scholars are committed to making a difference in ovarian cancer research.

Dr. Muneesh Tewari, Idea Development Award with Nested Teal Predoctoral Scholar

"This award has been an excellent opportunity for the Teal Predoctoral Scholar in my lab, Emily Knouf, to gain hands-on training in ovarian cancer research. She has already contributed to development of key methodology needed for a new approach for analyzing cellular heterogeneity in ovarian cancer. We hypothesize that such heterogeneity within ovarian cancers will be an important predictor of success or failure of treatments in individual patients."

~Dr. Muneesh Tewari, Principal Investigator, Fred Hutchinson Cancer Research Center

Ms. Patricia Goldman, Former IP Member, Ovarian Cancer National Alliance

"I'm an ovarian cancer survivor happily of 19 years. I'm a very fortunate person to survive this long. That unfortunately is not the case for many people. I think we bring the practical aspects. We know about toxicities of some treatments. So a scientist may look at a certain proposal and view it from the same point of what can this do in the laboratory, but when we look at something we say what's this going to do to the patient?"

Dr. Jian-Ping Wang, Translational Pilot Award with Nested Teal Predoctoral Scholar

"As a Teal Predoctoral Scholar, my responsibilities include the design, fabrication, and testing of spintronic sensors used in our research. These sensors are based on the same technology used to detect the magnetic field on a computer hard drive. In this case, the sensors will be used instead to detect the tiny field from magnetic nanoparticles chemically bound to protein biomarkers. My time will primarily be spent working in both the Nanofabrication Center and the Laboratory of Nanomagnetism and Quantum Spintronics under the guidance of Professor Jian-Ping Wang at the University of Minnesota."

"Previous ovarian cancer research shows a strong correlation between early detection and patient survival rate. This award gives us the chance to make a real impact on the efficacy of treatment by giving doctors the tools they need for early detection of ovarian cancer. I am very excited to have the chance to contribute as a Teal Predoctoral Scholar."

~Todd Klein, Teal Predoctoral Scholar, University of Minnesota

Game Changing Research

Significantly impacting the standard of care and/or challenging current paradigms in ovarian cancer.

Animal Models

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***

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***

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***

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. 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)***

Innovative Collaborations

Dr. David Bowtell: ***Multicenter, population-based resource involving collection of linked epidemiologic and clinical data and biospecimens from 1,859 cases and 1,073 matched controls (1,719 questionnaires, 1,694 blood samples, and 1,100 frozen tissue samples) to study ovarian cancer risk factors and biomarkers***

Dr. Andrew Berchuck: ***International Ovarian Cancer Association Consortium (OCAC) 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.***

In the Pipeline

Exceptionally promising early results in ovarian cancer research.

Drs. David Bowtell and Gillian Mitchell
Found that 44% of the 141 women with nonmucinous ovarian tumors carrying BRCA1/2 mutations did not have a family history of ovarian cancer or breast cancer.

Dr. Christine Walsh – Sensitizing Ovarian Cancer Cells
Demonstrated that Indole-3-Carbinol, a natural dietary phytochemical, sensitized multiple ovarian cancer cell lines to bortezomib, an FDA-approved treatment for other cancers.

Dr. Patricia Kruk – Urinary Bcl-2 Levels
Demonstrated that Bcl-2 is elevated in urine samples of ovarian cancer patients, regardless of tumor grade, stage, size, and subtype, and is potentially a noninvasive and low-cost way to detect ovarian cancer.

Dr. Christopher Crum – Precursor Evolution and Ovarian Cancer
Demonstrated that patients with serous cancer have many more SCOUTs (secretory outgrowths) in their fallopian tubes than patients whose fallopian tubes were removed for benign lesions. Along with the p53 signature, SCOUTs appear to serve as a surrogate precursor of ovarian cancer.

Dr. Kathryn Terry – Epidemiologic Predictors of Ovarian Cancer
Showed that women who took aspirin were at a reduced risk for nondominant ovarian tumors while women who took nonsteroidal anti-inflammatory drugs (NSAIDs) other than aspirin were at a reduced risk for dominant and nondominant ovarian tumors. Also found that women who were smokers were at an increased risk for both tumor types, but women who quit were only at increased risk for nondominant ovarian tumors.

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, an NSAID, as an inhibitor of small GTPase activation, epidermal growth factor receptor degradation, as well as ovarian cancer cell migration and invasion, making this NSAID a potential novel therapy for ovarian cancer metastasis.

Dr. Martina Bazzaro – Combination Therapy
Demonstrated that combining bortezomib and vorinostat resulted in apoptotic morphology in ovarian cancer cells but not in normal ovarian epithelial cells.

Dr. Bryan Toole – Novel Therapeutic Intervention to Reduce Chemoresistance
Showed that treatment with small oligomers of hyaluronan (a polysaccharide expressed at elevated levels in ovarian carcinoma's pericellular matrix) reversed resistance to doxorubicin and paclitaxel and may be a novel, nontoxic method of improving chemoresistance.

Dr. Brad Nelson – New Tools to Further Study Resistance
Developed a new bioinformatics program for assembling high-throughput sequence data and querying for the presence of single nucleotide variants (SNVs) in ovarian cancer.

Looking to the Future

Dr. Robert Kurman – Recently launched a multi-institutional, multidisciplinary consortium focused exclusively on early lesions in the fallopian tube as early events of ovarian high-grade serous carcinoma.

Dr. Laurence Cooper – Developing innovative technology to enhance the therapeutic potential of T cells by modifying them to express an ovarian cancer-specific chimeric antigen receptor.

Dr. Ramadeep Rattan – Investigating whether diet modulation will activate AMP-activated protein kinase and change the metabolic state of cancer cells to affect ovarian cancer progression and patient outcomes.

Dr. Ralph Weissleder – Optimizing, applying, and refining an innovative, diagnostic magnetic resonance platform to detect ovarian cancer cells and biomarkers.

Dr. Jian-Ping Wang – Developing sensitive, giant, magnetoresistive, nanoparticle-based sensors to detect serum biomarkers.

Dr. Animesh Barua – Developing an early detection test for ovarian cancer using markers in the blood and noninvasive, tumor-targeted ultrasound imaging with enhanced resolution.

Dr. Sally Kornbluth – Studying the regulation of ovarian cancer cell death by interrupting biochemical pathways to enhance responsiveness to chemotherapy.

Dr. Christopher Paige – 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 – Deciphering the adaptive immune response to ovarian cancer for future development of treatments to increase tumor immunity and patient survival.

Dr. Victoria Bae-Jump – Investigating the metabolic and endocrine effects of obesity on the pathogenesis of ovarian cancer.

Dr. Adam Karf – Studying the role of BORIS activation, a gene recently identified as being upregulated in EOC, in causing epigenetic and genetic changes.

Dr. Michael Birrer – 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.

Dr. Bo Rueda – Investigating whether oogonial stem cells, which are located at or adjacent to the ovarian surface epithelium, have the ability to form tumors with a phenotype similar to that of ovarian cancer.

Dr. Andre Lieber – Conducting preclinical studies to determine the safety and efficacy of JO-1, a small recombinant protein derived from adenovirus serotype 3, for the treatment of ovarian cancer in combination with selected chemotherapy drugs.

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7-2012