

CDMRP 
Department of Defense

Ovarian Cancer Research Program



U.S. Army Medical Research and Materiel Command



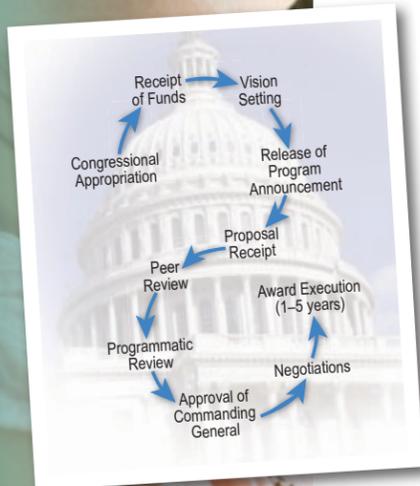
Congressionally Directed Medical Research Programs

History of the CDMRP

In 1992, the Office of the Congressionally Directed Medical Research Programs (CDMRP) was born from a powerful grassroots effort led by the breast cancer advocacy community that convinced Congress to appropriate funds for breast cancer research. This enabled a unique partnership among the public, Congress, and the military. Created within the U.S. Army Medical Research and Materiel Command to manage these critical funds, the CDMRP has grown to encompass multiple targeted programs and has received over \$5.8 billion in appropriations from its inception through fiscal year 2010 (FY10). Funds for the CDMRP are added to the Department of Defense (DOD) budget, wherein support for individual programs, such as the Ovarian Cancer Research Program (OCRP), is allocated via specific guidance from Congress.

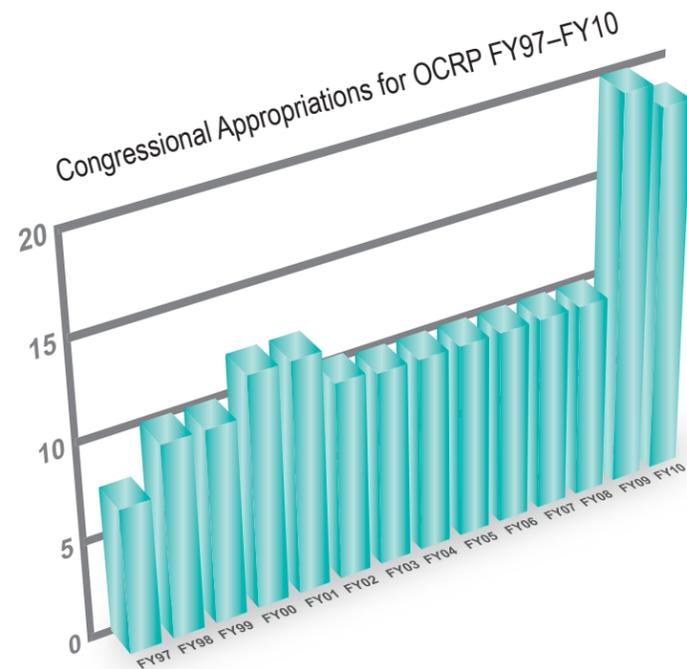
Proposal Review Process

The CDMRP uses a two-tier review process for proposal evaluation, with both steps involving dynamic interaction between scientists and disease survivors (consumers). The first tier of evaluation is a scientific peer review of proposals measured against established criteria for determining scientific merit. The second tier is a programmatic review, conducted by the Integration Panel, which compares proposals to each other and makes funding recommendations based on scientific merit, portfolio balance, and relevance to program goals.



Did you know?

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



Ovarian Cancer Research Program

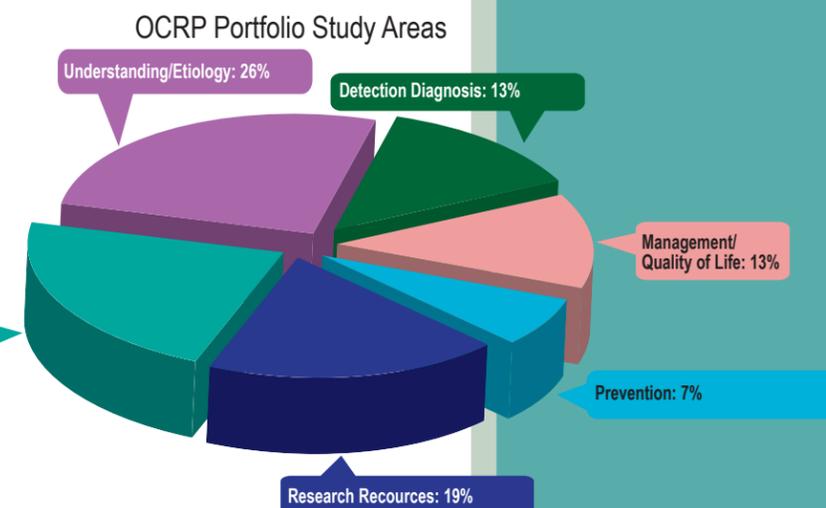
History of the DOD OCRP

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, efforts by ovarian cancer advocates to increase public awareness and federal funding for research have resulted in a total appropriation of nearly \$161M to the OCRP, including \$18.75M in FY10. The goals of the OCRP are adapted yearly to target critical research areas and to be responsive to the needs of the ovarian cancer community. The DOD OCRP is thinking differently about how to drive scientific progress in efforts to eliminate ovarian cancer. As a major leader in funding extramural ovarian cancer research, the DOD OCRP is investing in high-impact, innovative research that continues to fulfill unmet needs and move the field of ovarian cancer forward.

Key Initiatives of the DOD OCRP

- Support critical research resources
- Challenge and expand current thinking and approaches to ovarian cancer
- Support high-impact, innovative research that will lead to significant breakthroughs
- Facilitate multidisciplinary and nontraditional collaborations bringing diverse approaches and leveraging resources to accelerate the elimination of ovarian cancer
- Support partnerships between clinicians and laboratory scientists to accelerate the movement of promising ideas into clinical applications
- Foster the future generation of researchers focused on ovarian cancer

A total of 213 awards were made through FY09, and this FY10 Program Book demonstrates how much has been accomplished in the last 14 years of the DOD OCRP to accelerate research in achieving its mission.



VISION

Eliminate ovarian cancer.

MISSION

Support research to detect, diagnose, prevent, and control ovarian cancer.

Accelerating Discoveries Through Strategic Partnerships

Did you know?

- One in 71 women will develop ovarian cancer in her lifetime.
- In 2009, approximately 21,500 women in the United States were diagnosed with ovarian cancer, and an estimated 14,600 women died from this disease.

The success of the DOD OCRP can be attributed to the synergistic efforts of many talented and dedicated individuals. The strategic partnerships between the military, ovarian cancer consumer advocates, clinicians, and scientists have helped shape the DOD OCRP and accelerate the science. Through this partnership, the ovarian cancer consumer advocates work together with the scientists and clinicians to identify high-impact, innovative research that will lead to the elimination of ovarian cancer.

The two-tier review process utilized by the OCRP brings together the ovarian cancer survivors' firsthand perspectives with the expertise and knowledge of the scientists and clinicians on the peer and programmatic review panels. More than 500 scientists, clinicians, and ovarian cancer consumer advocates have participated in scientific peer review for the OCRP. The peer review panels, organized by scientific discipline, provide expert advice on the scientific and technical merit of research proposals as well as the impact of the proposed research on the early detection, prevention, treatment, and management of ovarian cancer. The OCRP Integration Panel, composed of scientists, clinicians, and consumer advocates who are leaders in their fields, provides vision for the OCRP. The Integration Panel refines program priorities and investment strategies that reflect the needs of the ovarian cancer community and makes funding recommendations that best meet the program's goals.

Ovarian cancer consumer advocate participation is a critical factor in the success of the DOD OCRP. The unique experiences of the consumer advocates complement the expertise of the scientists and clinicians who serve on both the peer and programmatic review panels. The voice of the ovarian cancer survivor brings a sense of urgency and the human dimension of the disease into the DOD OCRP's policy, investment strategy, and research focus. This perspective helps scientists and clinicians understand how the research

will impact the community, and moreover, encourages funding recommendations that reflect the concerns of consumer advocates and their families, as well as the clinicians who treat them.

Did you know?

- Since inception of the DOD OCRP, ovarian cancer survivors have participated in establishing the OCRP's priorities, research funding opportunities, and funding recommendations.
- More than 125 ovarian cancer survivors have participated as equal voting members at both scientific peer review and programmatic review.

"My anticipation to participate as a consumer reviewer was initially one of hesitation with only being an ovarian cancer survivor and patient advocate for 2 years. However, I discovered all my fears were unfounded. The support of my mentor was invaluable as her availability by e-mail or telephone was endless. This unwavering support continued through the process each step of the way by the program's staff. Without a doubt, this was an outstanding opportunity to learn and hear firsthand, as well as support with my vote, the most pioneering research demonstrating the quality and commitment of researchers in our country. To participate on the panel was an experience I will never forget, and not only extremely helpful in my advocacy work in San Diego, but inspiring hope of the possible breakthroughs in conquering this lethal cancer to save women's lives."

Ms. Peg Ford, Consumer Peer Reviewer



"I have had the opportunity to serve in a variety of capacities in the review of grant applications for the DOD OCRP over the years. Whenever asked to serve, I never for a moment hesitate to say yes. This is one program that truly adheres to its mission and has, and continues to have, a real and significant impact. It is a privilege to have been part of this program."

Dr. Linda Malkas, Peer Reviewer



"Being a peer reviewer for the DOD was an enriching and exciting experience. The information and assistance I received prepared me well for the panel discussions. The process and organization were well planned and easy to follow. My mentor was very helpful and friendly and gave me great advice along the way. All participants on the panel were professional and friendly. I was proud to serve my country and my fellow survivors by participating on the ovarian cancer panel. It was a unique opportunity as a citizen to be so closely involved in the democratic process. I am grateful to Congress, to the DOD, fellow citizens, and especially grateful to all the scientists and ovarian cancer researchers who are working to improve the lives of American women and all women around the world. As an ovarian cancer survivor, being involved in this process is truly the Pursuit of Happiness."

Ms. Lisa Sienkiewicz, Consumer Peer Reviewer





"As a 9-year survivor of late-stage ovarian cancer, I feel a deep sense of responsibility to work for positive change in the ovarian cancer community. There is no better place to direct my efforts than working with the Integration Panel of the DOD OCRP. To sit among scientists and physicians and have an equal say in every area.....WOW!" Ms. Mason testified before the DOD House Appropriations Subcommittee on May 20, 2010, on behalf of the Ovarian Cancer National Alliance, speaking to the need to fund research in ovarian cancer, particularly to better understand, diagnose, and treat the disease.

Ms. Karen Mason, Integration Panel Member



"The Department of Defense Ovarian Cancer Research Program is unique in providing the perspective of the patients whose very lives depend upon the outcome of the research that will be translated into new and improved therapies that are life extending."

Ms. Patricia Goldman, Integration Panel Member

Did you know?

- Ovarian cancer is the eighth most common cancer among women.
- Epithelial ovarian cancer is the most common type of ovarian cancer and accounts for 85% to 89% of ovarian cancers.
- Women diagnosed with early-stage ovarian cancer have a 5-year relative survival rate of ~93%.
- When diagnosed with late-stage ovarian cancer, the 5-year relative survival rate is 31%.

"The DOD OCRP is a uniquely flexible granting mechanism that has significantly expanded the opportunities for funding quality, cutting-edge ovarian cancer research."

Dr. Deborah Armstrong, Integration Panel Member

The Impact of the DOD OCRP

An Academy Dean, seven Early-Career Investigators, and their mentors launched the unique, interactive Ovarian Cancer Academy.

Developed OVA1™, the first IVDMA (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. This information will help physicians identify patients who should be referred to a gynecologic oncologist.

Discovered that MMP7 is elevated in serum up to 3 years prior to diagnosis of ovarian cancer.

Developed a targeted treatment using nanoparticles to deliver diphtheria toxin-encoding DNA to ovarian cancer cells, leaving healthy cells unaffected.

Validated SC144 (small molecule inducer) as a treatment for drug-sensitive and drug-resistant ovarian cancer.

Discovered API-2/tricirbine (now in Phase I clinical trials as VQD-002), a compound that potentially inhibits Akt-activated cancers, which includes over 40% of ovarian tumors.

Developed Anginex, a potent anti-angiogenic and anti-cancer peptide that shows efficacy in combating ovarian cancer.

Developed and patented treatment of ovarian cancer with squalamine in combination with other anti-cancer agents/modalities (now in Phase II clinical trials through Genaera Pharmaceuticals).

Demonstrated that enhancing the CD8+ T cell response to ovarian cancer results in tumor regression in 75% of cases without surgery or chemotherapy.

Showed that ovarian cancer cells are sensitive to glucose deprivation and resveratrol treatment when compared to control cells and that resveratrol can inhibit the PI3K/Akt/Tor pathway in ovarian cancer cells.

Discovered a panel of 13 promising genes that were selected for further validation as ovarian cancer biomarkers. Evidence showed that nine of these tumor vascular markers were expressed in the tumor vasculature in vivo, indicating that they are candidates for imaging or therapeutic targeting (patent is pending for the tumor vascular markers and methods of use thereof). Now in Phase I clinical trial.

OCRCP Is Moving the Field Forward...

The overall goal of the DOD OCRCP is to eliminate ovarian cancer by supporting innovative, high-impact research. In striving to achieve this goal, the OCRCP is promoting unique partnerships and fostering the next generation of investigators in ovarian cancer research. The OCRCP Consortium Award (released in spring 2010) will support a major multi-institutional research effort conducted by leading ovarian cancer researchers who specifically focus on identifying and characterizing early changes of disease associated with ovarian cancer.

The FY10 OCRCP is also concentrating on supporting early concepts that will continue to drive the field forward. The Pilot Award supports conceptually innovative, high-risk/high-reward research that could ultimately lead to critical discoveries or major advancements, while the Translational Pilot Award supports innovative translational research addressing a critical problem or question in ovarian cancer that will accelerate the movement of promising ideas toward clinical applications. Through these awards, the OCRCP is seeking innovative ideas that, if proven correct, will provide totally new paradigms, technologies, or applications that, when applied in the future, will reduce the burden of ovarian cancer.

“The unique strength of the Congressionally Directed Ovarian Cancer Research Program is that it greatly facilitates the germination and testing of new ideas and concepts that may not be otherwise considered by traditional funding mechanisms.”

Dr. Santo Nicosia, recipient of FY01 Program Project Award and FY09 Idea Development Award

OCRCP-Supported Development of Critical Research Resources

From the beginning, one of the main goals of the OCRCP was to establish shared resources to advance the study of ovarian cancer. Over the years, OCRCP investigators have produced several successful resources, including animal models, biomarkers, databases, critical tissue repositories, and computational tools.

| Principal Investigator | Research Resource |
|--|---|
| Dr. Nicole Urban | Repository with over 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. Samuel Mok | New biomarkers for early-stage ovarian cancer: osteopontin, protease M, and lysophosphatidic acid |
| Dr. Mary Daly | <i>Ovarian Cancer Risk-Reducing Surgery: A Decision Making Resource</i> (a book available at no cost to the public) |
| Dr. Gus Rodriguez and Dr. Patricia Johnson | Chicken models of ovarian cancer |
| Dr. David Bowtell | Multicenter, population-based resource involving collection of linked epidemiologic and clinical data and biospecimens from 2,003 cases and 1,073 matched controls (1,719 questionnaires, 1,694 blood samples, and 1,061 frozen tissue samples) to study ovarian cancer risk factors and biomarkers |
| Dr. Santo Nicosia | Ovarian cancer tissue repository with more than 600 samples |
| Dr. Louis Dubeau | Mouse model with homozygous BRCA1 knockout restricted to ovarian granulosa cells |
| 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. Tyler Jacks | Mouse model of ovarian cancer associated with endometriosis |
| Dr. Patricia Kruk | Bcl-2 as a urinary biomarker for ovarian cancer |
| Dr. Robert Kurman | New model of ovarian cancer that identifies two histological types of tumors – Types I and II Ovarian tumor tissue microarrays – 17 tissue microarrays comprising more than 500 tissues |
| 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. Georgia Chenevix-Trench | 1,839 ovarian epithelial and the fibroblast cell samples (675 ovarian cancer cases and 1,164 controls) |
| Dr. Rong Wu | Murine model of human ovarian endometrioid cancer |

Fostering the Next Generation of Investigators in Ovarian Cancer



In FY09, the OCRP released the program announcement for the Ovarian Cancer Academy Award, a virtual career development and research training platform consisting of Early-Career Investigator/Designated Mentor pairs from different institutions.

Integration Panel FY11 Chair-Elect, Dr. Michael Seiden said, "The Ovarian Cancer Academy is designed as a virtual academy that will bring together a group of like-minded, talented, and highly committed junior faculty with their mentors and an Academy Dean." Seven Early-Career Investigators were recommended for funding to launch this distinctive, interactive Academy that will be led by an Academy Dean.



"Reducing the burden of ovarian cancer requires recruiting and, more importantly, mentoring a group of scientists and clinicians who are committed to building sustained and productive careers in ovarian cancer research. Few academic medical centers or research centers have the large ovarian cancer research teams and the number of junior faculty focused on developing careers that are supported through peer-reviewed, competitively funded ovarian cancer research..."

Dr. Michael Seiden, Integration Panel Member



"It has been an exciting time in which to have had the privilege to lead the CDMRP's Ovarian Cancer Research Program. We have initiated the Ovarian Cancer Academy...The Academy is our newest investment into the future of ovarian cancer research and progress, funding the top pairs of dedicated ovarian cancer researchers with their upcoming young investigators in an interactive innovative research setting spanning basic, translational, and population science. We also see results of the investments of the OCRP over its more than 10-year history, helping women with ovarian cancer to live longer and live better as a result of the research ideas and programs that we have funded."

Dr. Elise Kohn, FY09-FY10 Integration Panel Chair

The Ovarian Cancer Academy



The Ovarian Cancer Academy puts the African proverb, "It takes a village to raise a child" into action for training the next generation of ovarian cancer researchers.



RETURN ON INVESTMENT:

Supporting Collaborative Research

Offered in FY97–FY98 and FY00–FY01, the intent of Program Project Awards was to enhance ovarian cancer research infrastructure by establishing collaborations across research disciplines and institutions, supporting innovative research, and attracting new independent investigators into the ovarian cancer research field. Over a decade later, results from the Program Project Awards continue to have an impact on ovarian cancer research.

Dr. Nicole Urban, FY97 Program Project Award Fred Hutchinson Cancer Center

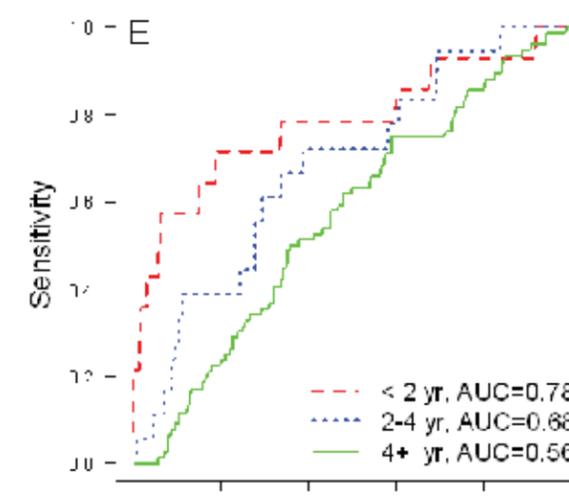
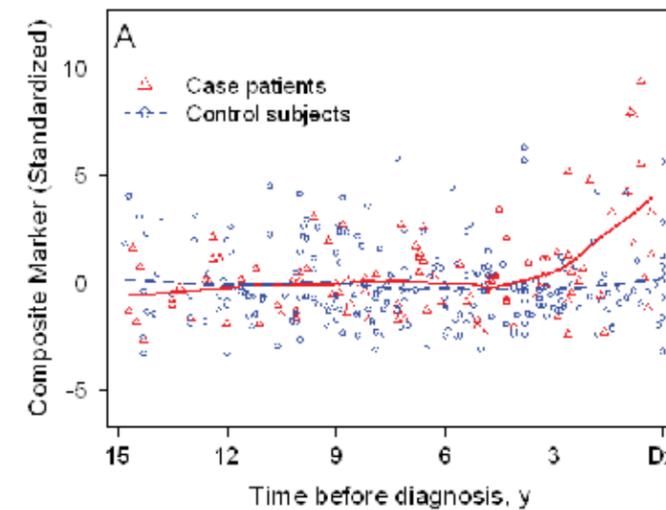
Women are typically diagnosed with advanced stage ovarian cancer, as it is frequently without overt or specific symptoms until late in its development. Identifying a screening strategy to reduce mortality from ovarian cancer through early detection has been Dr. Urban's goal since 1994. Her current program in translational ovarian cancer research at the Fred Hutchinson Cancer Center was built on work funded by the DOD OCRP. Working with Drs. Beth Karlan at Cedars-Sinai and Leroy Hood at the University of Washington, she identified novel ovarian cancer biomarkers including HE4, Mesothelin (MSLN), and secretory leukocyte protease inhibitor.

Dr. Urban developed assays to measure in serum both HE4 (an epididymal gene consistently overexpressed in ovarian malignancy but not in normal or benign ovarian tissue) and MSLN (a 40-kDa glycoprotein present on the surface of malignancies including the majority of mesotheliomas and ovarian cancers). The original plate-based HE4 and MSLN assays have been licensed to Fujirebio Diagnostics Inc. (FDI), a diagnostics company that received FDA approval for HE4 as a recurrence monitoring marker. FDI markets MSLN (as MesoMark) in Australia as a diagnostic marker for mesothelioma. Using specimen-efficient bead-based assays, Dr. Urban has evaluated top markers in preclinical samples to learn which markers give early signal.

Working with Dr. Garnet Anderson, she found that a composite marker calculated as the maximum of CA125, HE4, and MSLN begins to separate cases from controls over 4 years prior to diagnosis. Dr. Urban is leading the Novel Markers Trial, a prospective randomized Phase I screening trial in high-risk women, in collaboration with Drs. Karlan, Jonathan Berek (Stanford), Melanie Palomares (City of Hope), and Pam Paley (Swedish Medical Center).

The Program Project led to NCI funding in 1999 for the Pacific Ovarian Cancer Research Consortium (POCRC) SPORE in ovarian cancer. The DOD OCRP and NCI funding allowed for development of resources for translational ovarian cancer research including collection, management, and allocation of tissue and blood samples from

women with ovarian cancer, with benign ovarian conditions, and with healthy ovaries. The DOD OCRP grant provided the foundation for what is now a mature specimen repository that has accelerated the progress of over 140 scientists at many academic institutions and industry.



Lowess curves of standardized marker levels by time before diagnosis or reference date (A) and corresponding receiver operating characteristic curves by time before diagnosis (E) for composite marker (defined for each observation on each woman as the sum of her CA125, human epididymis protein 4 [HE4], and mesothelin levels).

From: Anderson GL, McIntosh MW, Wu L, Barnett M, Goodman G, Thorpe JD, Bergan L, Thornquist MD, Scholler N, Kim N, O'Briant K, Drescher C, Urban N. Assessing Lead Time of Selected Ovarian Cancer Biomarkers: A Nested Case–Control Study. *J Natl Cancer Inst.* 2010 Jan 6;102(1):26–38. PMID: PMC2802285

Her DOD OCRP Program Project Award provided Dr. Nicole Urban with the foundation for her ovarian cancer research:

Received POCRC SPORE in ovarian cancer

Supported by SPORE grant twice competitively renewed

Received SPORE program Leadership Award in 2005

Four recipients of Program Project Awards—The University of Texas MD Anderson Cancer Center, Fred Hutchinson Cancer Research Center, Fox Chase Cancer Research Center, and Brigham and Women's Hospital—were subsequently awarded National Cancer Institute (NCI) Specialized Program of Research Excellence (SPORE) grants to further support translational research approaches to this disease.

RETURN ON INVESTMENT:

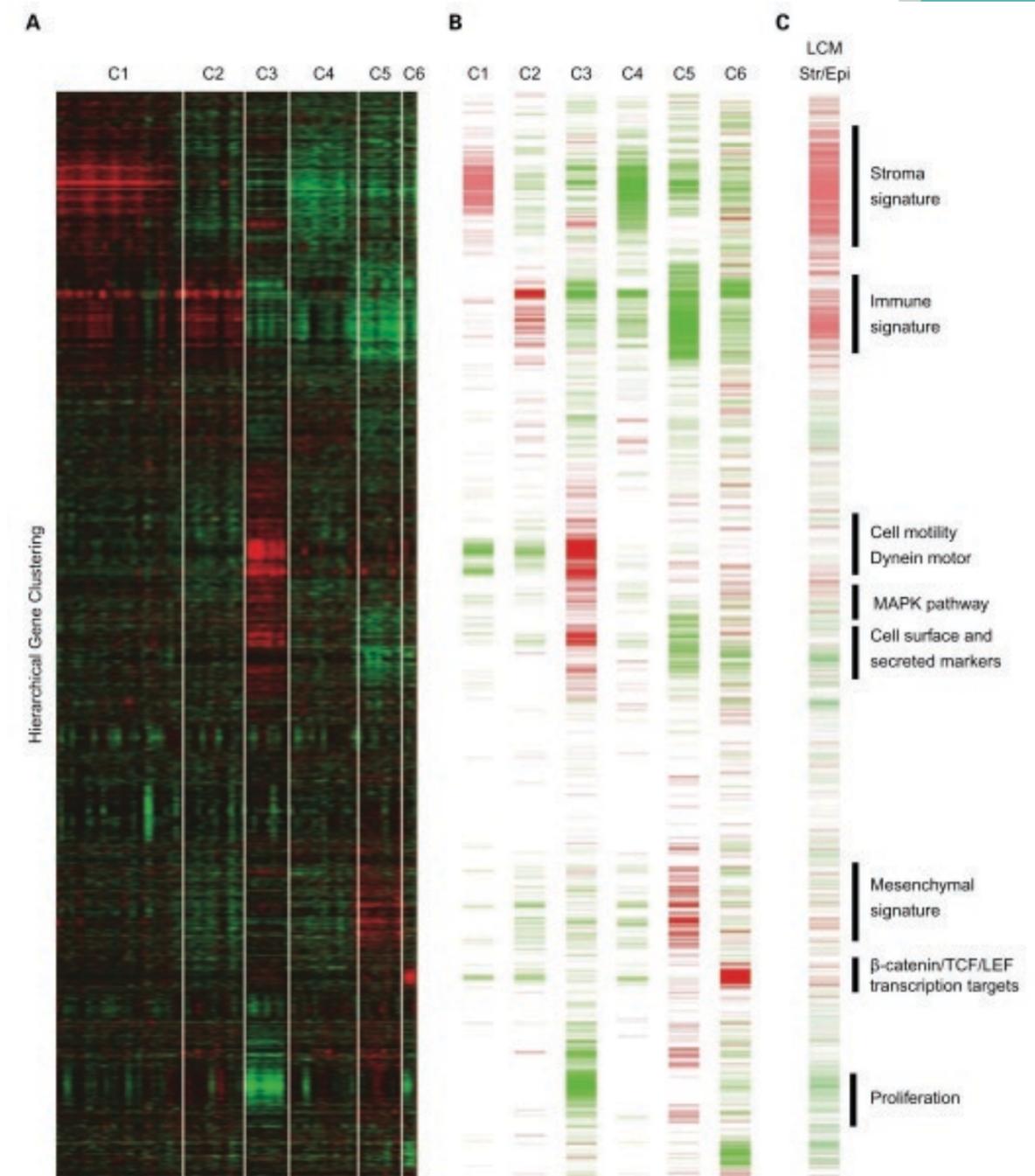
Supporting Collaborative Research

Dr. David Bowtell, FY00 Program Project Award Peter MacCallum Cancer Centre

A major obstacle to preventive strategies for ovarian cancer is the lack of recognized modifiable risk factors. Dr. David Bowtell, from the Peter MacCallum Cancer Centre in Melbourne Australia, studied the molecular epidemiology of ovarian cancer. He and his colleagues formed the Australian Ovarian Cancer Study (AOCS), a population-based cohort of over 2,000 women with ovarian cancer. With a bank of over 1,100 fresh frozen tumors, hundreds of formalin-fixed, paraffin-embedded blocks, and very detailed clinical follow-up, AOCS has enabled over 60 projects since its inception, including international collaborative studies in the United States, United Kingdom, and Canada. AOCS has facilitated approximately 40 publications, including those of the founding investigators, most of which have been released in the past 2 years. Findings resulting from AOCS projects include the identification of:

- Differences in epidemiological risk factors between ovarian, fallopian, and primary peritoneal cancer (*International Journal of Cancer* 2008)
- New ovarian cancer susceptibility loci (*Nature Genetics* 2009)
- Association between MDR1 genotype and progression-free survival in optimally debulked patients (*Clinical Cancer Research* 2008)
- Novel molecular subtypes of serous ovarian cancer associated with clinical outcome (*Clinical Cancer Research* 2008)
- Distinct mechanisms of primary treatment failure in serous ovarian cancer (*Clinical Cancer Research* 2009)

Since the initial OCRP award, AOCS has also been supported by Australian National Health and Medical Research Council (NHMRC), state-based Cancer Council, and Cancer Australia. AOCS was recently chosen by the NHMRC to contribute to the International Cancer Genome Consortium effort. In 2007, Dr. David Bowtell and Dr. Gillian Mitchell were awarded an OCRP Translational Research Partnership Award to examine the frequency of BRCA1 and BRCA2 mutations in the AOCS. Without award of the OCRP Program Project grant, this powerful enabling resource for ovarian cancer research would not have been created.



Clustering of expression data derived from serous and endometrioid tumors originating from the ovary, peritoneum, and fallopian tube. A, a series of 251 from 285 tumors were robustly clustered or classified into six k-means groups (C1–C6). Average linkage hierarchical clustering using a Pearson correlation metric was used to cluster genes based on relative expression across the 251 cancers. Per gene median normalization was used for visualization. B, differentially expressed genes identified by SAM analysis. Genes ordered to show relative position within the hierarchical cluster from A. Green, showing relative under expression; red, relative overexpression. C, differentially expressed genes identified by profiling LCM captured cells from tumor and stroma representing C1 tumor specimens. Genes are ordered based on relative position within the hierarchical cluster (A). Red, overexpressed in stroma; green, overexpressed in the tumor.

Richard W. Tothill, Anna V. Tinker, Joshy George, Robert Brown, Stephen B. Fox, Stephen Lade, Daryl S. Johnson, Melanie K. Trivett, Dariush Etamadmoghadam, Bianca Locandro, Nadia Traficante, Sian Fereday, Jillian A. Hung, Yoke-Eng Chiew, Izhak Haviv, Australian Ovarian Cancer Study Group, Dorota Gertig, Anna deFazio, and David D.L. Bowtell. 2008. Novel molecular subtypes of serous and endometrioid ovarian cancer linked to clinical outcome. *Clin Cancer Research* 14(16):5198-208.

RETURN ON INVESTMENT:

Supporting Collaborative Research



Dr. Santo Nicosia, FY01 Program Project Award University of South Florida

Eighty to 85% of ovarian tumors arise from the otherwise inconspicuous tissue that covers the outer aspect of the ovary, the so-called ovarian surface epithelium. Dr. Nicosia was awarded an OCRP Program Project Award to investigate the mechanisms of ovarian cancer development and progression with the ultimate goal to identify potential targets for therapeutic intervention.

Dr. Nicosia and his colleague Dr. Jin Cheng discovered API-2/triciribine, a small molecule Akt pathway inhibitor that potently inhibits Akt-activated cancers, which includes over 40% of ovarian tumors. In 2005, VioQuest Pharmaceuticals acquired the licensing rights to API-2/triciribine. Now called VQD-002, this compound is in Phase I clinical trials and has been found to be synergistic with various cancer therapies.

Another collaborating PI, Dr. Patricia Kruk, found that Bcl-2, an anti-apoptotic protein, could be detected in the urine of ovarian cancer patients. Her findings provided the data for Dr. Kruk to subsequently be awarded an OCRP Idea Development Award to determine if Bcl-2 could be used as a urinary biomarker for the detection of ovarian cancer. Dr. Kruk continues to receive funding and produce exciting results including a recent finding that Bcl-2 can be detected in the urine of women at risk for ovarian cancer indicating that this biomarker may be utilized for the identification of at risk women. Dr. Kruk has applied for a patent to develop a device for urinary detection of ovarian cancer.

Did you know?

- **Ovarian cancer survivors collaborate on OCRP team-oriented award mechanisms.**

Dr. Andrew Berchuck, FY97 Program Project Award The International Ovarian Cancer Association Consortium

From the Researcher's Perspective:

In 1997, our research group at Duke University was awarded an OCRP Program Project Award to investigate the biological basis for chemoprevention of ovarian cancer. In 2001, we were awarded another Program Project Award to continue this research.

Although inherited BRCA1 and BRCA2 mutations are responsible for about 10% of ovarian cancer cases, these mutations are carried by less than 1% of the population. Other genetic factors likely exist that increase risk moderately, and by virtue of being more common, they may account for a significant fraction of cases. One of the aims of our program project grant was to perform an ovarian cancer genetic association study to identify common low penetrance risk alleles. Over 1,300 cases and an equal number of age- and race-matched control subjects were accrued to the North Carolina Ovarian Cancer Study.

Although we were thrilled by the enthusiasm with which our study was embraced locally, it became apparent that much larger studies would be needed. As our DOD program project was ending in 2005, my colleague, Dr. Joellen Schildkraut, and I had the opportunity to help lead the formation of an international Ovarian Cancer Association Consortium (OCAC) that is now composed of over 20 groups. The consortium meets biannually and is working together to identify and validate single nucleotide polymorphisms (SNPs) that affect disease risk through both candidate gene approaches and genome-wide association studies (GWAS). OCAC reported last year in *Nature Genetics* the results of the first ovarian cancer GWAS, which identified an SNP in the region of the BNC2 gene on chromosome 9 (*Nature Genetics* 2009;41:996-1000).

We envision a future in which reduction of ovarian cancer incidence and mortality will be accomplished by implementation of screening and prevention interventions in women at moderately increased risk. Such a focused approach may be more feasible than population-based approaches, given the relative rarity of ovarian cancer.



FIVE YEARS LATER:

The FY05 Pilot Awards

For FY05, the DOD OCRP offered the Pilot Award, a mechanism aimed at supporting highly innovative, high-risk/high-reward ovarian cancer research that focused on etiology/tumor biology or preclinical development of targeted therapies or early detection/diagnosis of ovarian cancer. Seven awards were made, and below are the research results that five of the investigators accomplished through this mechanism.

Crowd Control of Ovarian Cells **Dr. Carrie Rinker-Schaeffer, University of Chicago**

Metastasized ovarian cancer is difficult to eliminate, and the biochemical and biological mechanisms of metastasis are mostly unknown. Dr. Carrie Rinker-Schaeffer of the University of Chicago is approaching this mechanism from a novel perspective: she conducted the first tests of quorum-sensing behavior in ovarian cells. By applying the behavior of bacterial populations to ovarian cancer, Dr. Rinker-Schaeffer is testing the hypothesis that the quorum-sensing mechanism is involved in metastatic colonization in ovarian cancer. Specifically, she observed that MKK4 expression has a quorum-dependent function in ovarian cancer cells that causes a reversible cell cycle arrest at the metastatic site. Based on her findings, Dr. Rinker-Schaeffer created a working model of metastatic colonization in four steps: (1) cells move from the primary tumor and attach to the secondary target structures; (2) cell adhesion/survival/proliferation occurs; (3) surviving cells form microcolonies (aggregates); and (4) cells proliferate, resulting in overt metastases. Her research also led to the formation of the Collaborative Working Group on Bacterial Biofilms and Cancer Metastasis, a unique, multidisciplinary organization of scientists that explores the parallels between bacterial biofilms and cancer metastasis.

“Basically, the DOD funding helped me get our work started. I realized, however, in order to launch what is essentially a new field that I needed to bring a team of scientists who have different expertise together. So that’s what I’ve done.”

Dr. Carrie Rinker-Schaeffer, FY05 Pilot Award and FY08 Idea Development Award

Validating the Gallus domesticus Model **Dr. Dale Hales, Southern Illinois University School of Medicine**

Research into the cause of ovarian cancer has been severely hampered by lack of suitable animal models. Ovarian tumors are rarely observed in most species with the notable exception of the human and the domestic hen, which, like humans, spontaneously develops ovarian cancer. Despite the marked similarities of the development of ovarian cancer in aging hens compared to humans, there has been relatively little research that has exploited the domestic hen as a model for studying ovarian cancer. This award validated the use of the egg-laying hen as a model. In hens ages 1–5 years, the presence of all four types of ovarian tumors analogous to human ovarian cancer were histologically confirmed. Microarray results from the chicken ovarian tumors were uploaded into the Oncomine™ search engine and compared to human data. The human and chicken genomes shared downregulated and upregulated genes, and several of these genes (MAP kinase 8, TGF-beta, MMP15, Wnt-11, and RAB1A) have recognized roles in cancer biology. CYP1B1, a cytochrome P450 enzyme, was found to have a pattern of expression in the hen ovary, making it a potential target for the prevention/treatment of ovarian cancer as well. With his collaborator, Dr. Judy Luborsky of Rush University Medical Center, Dr. Hales demonstrated that selenium-binding protein 1 (SELENBP1) is expressed in normal ovaries and ovarian tumors in the hen model, and its expression was shown to be reduced in hen ovarian tumors as has been observed in human ovarian tumors. The expression of mRNA and protein of two cyclooxygenase enzyme isoforms, COX-1 and COX-2, were shown in the post-ovulatory follicle in hens for the first time. Additionally, Drs. Hales and Luborsky identified antitumor antibodies in the hen model of ovarian cancer that are similar to those found in human ovarian cancer.



FIVE YEARS LATER:

The FY05 Pilot Awards

Overcoming Resistance to Endocrine Therapy Dr. Ratna Vadlamudi, University of Texas Health Science Center at San Antonio

Despite the epidemiological evidence supporting a role of estrogen in the ovarian cancer progression, the response to hormonal therapy using selective estrogen receptor modulators is only observed in 10%–15% of cases. Dr. Ratna Vadlamudi first demonstrated the contribution of proline glutamic acid and leucine-rich protein 1 (PELP1) to the tumorigenic potential in ovarian cancer cells. PELP1, a novel estrogen receptor coactivator protein, may be involved in the resistance of ovarian tumors to endocrine therapies. Dr. Vadlamudi's research team showed that PELP1 functions as a novel proto-oncogene in ovarian cancer cells and plays an essential role in the activation of c-Src, and AKT pathways. These results indicate that the PELP1-Src-AKT axis could be used as a potential diagnostic or therapeutic target in ovarian cancer.

Dr. Vadlamudi also developed novel PELP1 siRNA liposomes that can be used to decrease PELP1 expression and reduce ovarian tumor cell growth in animal models. The downregulation of PELP1 sensitized ovarian cancer cells to carboplatin and paclitaxel, suggesting that targeting PELP1 could enhance the potency of chemotherapy drugs.

New Links Between Genomic Instability and Cilia Dr. Erica Golemis, Fox Chase Cancer Center

Dr. Erica Golemis of the Fox Chase Cancer Center investigated the contribution of HEF1 (also known as NEDD9) and Aurora A to genomic instability and the metastatic properties of ovarian cancer. She established that an important function of both HEF1 and Aurora A is in the control of centrosome numbers and that HEF1 interacts with Ajuba, a scaffolding protein, to activate Aurora A in this process. Dr. Golemis and her team also showed that HEF1-dependent Aurora A activation induced disassembly of cilia (centrosome-derived organelles through which cells sense the microenvironment) through activation of HDAC6, a histone deacetylase. In collaboration with other Fox Chase researchers, Dr. Golemis also observed a correlation between HEF1 and phospho-Aurora in low- and high-grade serous epithelial ovarian cancer tumors. Separate studies have shown that (1) HEF1 was commonly overexpressed in aggressive cells and tumors of multiple lineages but also that (2) reducing HEF1 expression in a knockout mouse model was associated with centrosomal abnormalities and aneuploidy and changes in tumor incidence. Dr. Golemis and her team are currently assessing the manipulation of HEF1 for ovarian tumor development and believe that the HEF1 protein will be recognized as an important biomarker in ovarian cancer progression.

A Potential Target for Therapeutic Interventions Dr. Xiaoyuan Chen, Stanford University

Dr. Xiaoyuan Chen of Stanford University is using high resolution microPET (position emission tomography) to image ovarian cancer integrin $\alpha\beta3$. Integrin $\alpha\beta3$ is expressed at a higher rate in primary ovarian cancers than ovarian tumors with low malignant potential, indicating that it may have a role during ovarian cancer progression and could be a target for therapeutic interventions. Dr. Chen and his team have developed peptide tracers for PET imaging in mice with high affinity and specificity for integrin $\alpha\beta3$. He established ovarian cancer models with differentiated integrin levels and found that one of the peptide tracers has high tumor targeting efficacy in vivo. An exploratory Investigational New Drug application submitted to the FDA has been approved and the first in-human studies have been conducted.

A representative whole-body PET image of a healthy volunteer is shown. He is now a senior investigator and lab chief at the Laboratory of Molecular Imaging and Nanomedicine (LOMIN), National Institute of Biomedical Imaging and Bioengineering (NIBIB), National Institutes of Health (NIH).



Representative projection PET image of a healthy volunteer injected with ^{18}F -labeled RGD peptide tracer ^{18}F -FPPRGD2.



"I found the DOD Integration Panel a breath of fresh air with the scientists on the panel from diverse backgrounds, which made for a well-rounded group but most importantly with the ability to think outside the box. The ideas that were developed were exciting and could be immediately translated into the next grant cycle, which allows for rapid translation to research. Overall a pleasure and an honor."

Dr. Molly Brewer, Integration Panel Member

Early Detection and Diagnosis

Affinity-Based Serum Proteomics for Ovarian Cancer Early Diagnosis

Dr. Martin McIntosh, Fred Hutchinson Cancer Research Center

With the goal of identifying biomarkers for the early detection of ovarian cancer, Dr. Martin McIntosh, an FY05 Idea Development Award recipient, and colleagues, Drs. Paul Lampe and Nathalie Scholler, are taking advantage of the unique characteristics of phage and yeast recombinant antibody libraries and using them as the basis for serum biomarker discovery. The group found that identifying ovarian cancer markers based on their behavior in both tissue and plasma is far superior to using tissue alone or plasma alone. They identified distinctive binding sequences that bind to ascites but not to peritoneal fluid from healthy women and then identified those that also preferentially bind to plasma from ovarian cancer patients compared to plasma from healthy women. Forty putative biomarkers have been identified and are undergoing validation using enzyme-linked immunosorbent assay or mass spectrometry-based methods.

One potential novel protein biomarker, PEBP1, identified via both mass spectrometry and microarray-based approaches, was detected in 29 of 30 ascites samples and discriminated ovarian cancer sera from that of healthy women or women with benign cysts. PEBP1 is undergoing further validation as a protein biomarker for early detection of ovarian cancer. Two other markers (MMP7 and IGFBP2) have been measured in preclinical serum samples, those collected months and years before cancer diagnosis to determine which may elevate prior to disease. Although based on a small sample size, MMP7 may identify 25% of cases at 95% specificity 3 years before ovarian cancer diagnosis. Although MMP7 has a lower sensitivity than CA-125, it appears to complement both CA-125 and HE4 and may provide information pertaining to risk earlier.

The Development of OVA1™

Dr. Zhen Zhang, Johns Hopkins University

Dr. Zhen Zhang, with funding from an FY03 Idea Development Award, discovered and validated a panel of ovarian cancer biomarkers for the early detection of ovarian cancer that have been patented and licensed by Vermillion, Inc. (formerly CIPHERGEN). Based on these discoveries, Dr. Zhang and colleagues at Johns Hopkins University, in collaboration with Vermillion, have developed a test, OVA1, that can help physicians detect ovarian cancer in a pelvic mass prior to surgery. This information will help physicians identify patients whose surgeries should be referred to a gynecologic oncologist. OVA1 is the first IVDMIA (in vitro diagnostic multivariate index assay) of proteomic biomarkers cleared by the FDA for clinical use.



Targeting Ovarian Cancer

Anginex: Inhibiting Angiogenesis in Ovarian Cancer

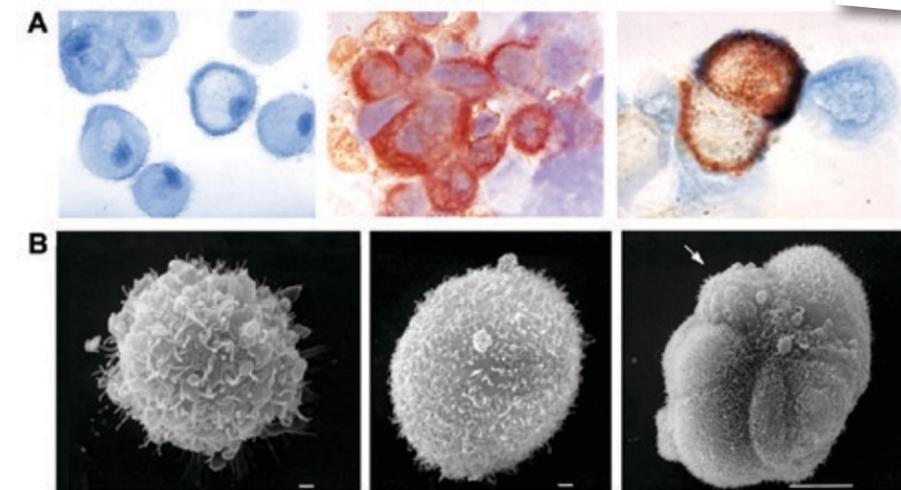
Dr. Sundaram Ramakrishnan, University of Minnesota

Anginex, a potent anti-angiogenic and anti-cancer peptide, was developed and patented by principal investigators funded through Dr. Sundaram Ramakrishnan's FY98 Program Project Award. Anginex and its improved analogs were found to not only inhibit angiogenesis in ovarian cancer, but also to potentiate existing chemotherapy and radiation therapies. PepTx, Inc., founded by Dr. Ramakrishnan's Program Project collaborator, Dr. Kevin Mayo, produces Anginex, which is marketed by Phoenix Pharmaceuticals.

Individualized Vaccines for Ovarian Cancer

Dr. Jianlin Gong, Boston University

Dr. Jianlin Gong, with funding from an FY99 Idea Award, developed a vaccine for ovarian cancer by fusing dendritic cells to patient-derived ovarian tumor cells. This design has resulted in a vaccine that stimulates the patient's immune system to generate an immune response against its own tumor. Dr. Gong and collaborators aim to test this vaccine for the treatment of ovarian cancer.



Fusion of dendritic cells (DC) with ovarian cancer (OVCA) cells. (A) Cytochrome preparations of DC (left panel), OVCA (middle panel), and DC/OVCA fusions generated from patient-derived sample (right panel). Cells were stained with anti-HLA-DR, (blue color) and anti-CA-125 (red color) antibodies (magnification, x60). (B) Surface structure of DC, OVCA, and DC/OVCA fusion cells examined by scanning electron microscope (SEM, x4800).

Did you know?

- Pregnancy and taking birth control pills both lower the risk of ovarian cancer.

Targeting Ovarian Cancer

Enhancing the Effectiveness of Chemotherapy Dr. Richard Pietras, University of California, Los Angeles

Dr. Richard Pietras, with funding from an FY99 Idea Award, demonstrated that squalamine, an anti-angiogenic steroid, inhibits ovarian tumor growth by inhibiting tumor-associated blood vessel formation. Treatment with squalamine was also found to enhance the effects of cisplatin and carboplatin chemotherapy. In partnership with Genaera Pharmaceuticals, Dr. Pietras' research progressed to Phase II clinical trials, but lack of funding for more costly Phase III trials has stalled development of this therapy.

LPA-Blocking Monoclonal Antibodies: Promising Treatments for Ovarian Cancer

Dr. Gordon Mills, University of Texas MD Anderson Cancer Center

Dr. Gordon Mills received an FY02 Idea Development Award to develop a method to detect lysophosphatidic acids (LPA) in serum. LPA contributes to the poor outcome of ovarian cancer by increasing its ability to grow and survive and, in addition, to spread across the peritoneal cavity. It also decreases the activity of the most commonly used drug in ovarian cancer, cisplatin. Two promising drug candidates emerged from Dr. Mills' award and are currently being developed by Lpath, Inc., a biotechnology company founded by Dr. Mills' collaborator, Dr. Roger Sabbadini (Dr. Mills is the chair of Lpath's scientific advisory board). ASONEP (Sonepcizumab), a humanized monoclonal antibody to sphingosine-1-phosphate, has been shown in preclinical studies to reduce tumor volume and metastasis and is currently in Phase I clinical trials for the treatment of advanced solid tumors. This drug, which has shown promising results against several cancers and multiple sclerosis, is also in Phase I clinical trials as iSONEP, for the treatment of age-related macular degeneration. Lpathomab, a humanized monoclonal antibody to LPA, has also demonstrated promising anti-angiogenic and anti-metastatic activity and is under development by Lpath for the treatment of ovarian cancer and other tumor types.



On the Horizon

CONCEPT AWARDS—EXPLORING INNOVATIVE CONCEPTS AND THEORIES IN OVARIAN CANCER

Detecting Circulating Ovarian Cancer Cells by High-Throughput Microscopy Dr. Kristiina Vuori, Burnham Institute for Medical Research

The vast majority of women diagnosed with ovarian cancer present with advanced disease and of these women, 50%–70% will face a recurrence of their disease and a survival rate of only 29%. It is now known that colonization of micrometastatic epithelial cells from the circulating peripheral blood to the bone marrow correlates with to an increased risk for future relapse and decreased survival in many cancers including ovarian cancer. Unfortunately, there is no reliable tool to screen for or diagnose ovarian cancer or to monitor for its recurrence. Detection of tumor cells in the peripheral blood may provide an avenue for the development of such a tool. However, heterogeneity of tumor cell genetic and expression markers and the rarity of these cells in the blood have challenged the development of a reliable detection method.

Dr. Vuori and her collaborator Dr. Jeffrey Price, with funding from an FY06 Concept Award, have developed an automated microscopy-based technology to detect these metastatic cancer cells within the peripheral blood by using cellular morphometric features that are common to all cancer cells.

For initial experiments, human cancer cells expressing green fluorescent protein were mixed with normal human endothelial cells and hematopoietic cells. Using two nuclear morphometry characteristics, nuclear size, and wiggle (eccentricity), cancer cells were detected with a sensitivity of 88%, which was confirmed by cancer cell fluorescence. A true positive rate of 90% represents excellent performance for a cancer diagnostic test. Expanding the morphological parameters used for classification to seven, Drs. Vuori and Price developed an algorithm that was able to detect cancer cells with a sensitivity of 92.1% and a specificity of 96.5%. These results enabled them to secure additional funding to validate the algorithm in vivo in future studies. This technology has the potential to help clinicians detect ovarian cancer earlier, more easily, and more accurately and has the added potential of being applicable to other cancers.



On the Horizon

CONCEPT AWARDS—EXPLORING INNOVATIVE CONCEPTS AND THEORIES IN OVARIAN CANCER

Naproxen Interferes with Ovarian Cancer Cell Invasion and Migration

Dr. Laurie Hudson, University of New Mexico

Dr. Laurie Hudson of the University of New Mexico hypothesized that regulating protein trafficking could be a novel therapeutic strategy to modify surface levels and localization of cancer-relevant proteins. Epidermal growth factor receptor (EGFR) is overexpressed in ovarian cancer and is associated with poor prognosis. The study goal was to identify small molecule modulators of Rab function that will promote EGFR trafficking toward degradative compartments with the goal of preventing persistent signaling or receptor recycling to the cell surface with subsequent reactivation. Specifically, she collaborated with an NIH Roadmap Molecular Libraries Screening Center to test small molecule inhibitors or activators of Rab5 and Rab7 for impact on EGFR trafficking. Dr. Hudson used the nonsteroidal anti-inflammatory agent, naproxen, to activate Rab7 and Rab5 in the EGFR model. She discovered that naproxen regulates Rab activation in vitro and in vivo, leads to retention of the EGFR receptor in cells rather than degradation, and selectively inhibits ovarian tumor cell migration with no impact on cell proliferation or apoptosis. Her findings could provide a new therapeutic drug target for ovarian cancer, and she intends to expand her studies into preclinical models.

Determining the Role of microRNAs in Chemoresistance

Dr. Jin Cheng, H. Lee Moffitt Cancer Center

Dr. Jin Cheng of the H. Lee Moffitt Cancer Center evaluated the importance of microRNAs (miRNA) in ovarian cancer chemoresistance. Dr. Cheng's research team identified and verified a panel of miRNAs that are deregulated in cisplatin- and taxol-resistant ovarian cancer cells. They further characterized two miRNAs that are upregulated in chemoresistant cells, miR-214 and miR-221/222. Dr. Cheng's team found that expression levels of miR-214 and miR-221/222 are inversely related to overall survival. Both have a role in chemoresistance by targeting the PTEN and pro-apoptotic protein PUMA, to enhance cell survival. Knockdown of miR-221 or/and miR-222 in CDDP resistant A27080CP cells significantly enhanced cell death induced by CDDP compared to scrambled oligo-treated cells. Dr. Cheng additionally identified another miRNA expressed in ovarian tumors, miR-200a, as being oncogenic. miR-200a also induces chemoresistance, and knocking it down induced apoptosis in cisplatin-sensitive and cisplatin-resistant cells. Overall, these results suggest that these miRNAs could be important therapeutic targets for overcoming chemoresistance in ovarian cancer.



Using the Egg-Laying Hen as a Model

Dr. Judith Luborsky, Rush University Medical Center

Using egg-laying hens as a spontaneous model of ovarian cancer, Dr. Judith Luborsky of the Rush University Medical Center examined whether hens with auto-ovarian auto-antibodies (AOA) are more likely to develop ovarian cancer. In women, AOA are associated with infertility and are an epidemiologic risk factor for ovarian cancer. Dr. Luborsky found that hens with AOA showed significant evidence of neo-angiogenesis, a surrogate marker of ovarian cancer. Additionally, she observed that specific antibodies to mesothelin, an antigen in human ovarian cancer, were found in hens with ovarian tumors. Dr. Luborsky's



research has shown that AOA may be a predictor of ovarian cancer that could be used to develop a test for the detection of ovarian cancer in its earlier stages.



"As a consumer reviewer on the ovarian cancer panel, I gained three very important things. First, I was able to report back to the ovarian cancer patient population I represent that hope is not just a word; it is being backed up with money and research, research that holds real promise for a screening test and more effective treatments for this deadly disease. Secondly, I witnessed a mutual respect between the scientists and the consumer reviewers. I was able to understand where they felt the research should go next and I was able to convey to them what ovarian cancer survivors really want to see happen sooner than later. Without exception they expressed understanding of my views and in some cases shifted focus from one proposal to another based on the input from me and other consumer reviewers. Lastly, my experience strengthened my resolve to work diligently to get increased funding through Congress for ovarian cancer research and awareness programs."

Ms. Susan Leighton, Consumer Peer Reviewer





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