

## DoD Ovarian Cancer Research Program (OCRP)

*Each year, the Department of Defense's office of the Congressionally Directed Medical Research Programs (CDMRP) assesses scientific opportunities to advance research in specific areas. The investigators supported by individual programs are making significant progress against targeted diseases, conditions, and injuries. This list is not intended to be a full representation of accomplishments, but rather a sampling of the broad portfolio of research and advances resulting from congressional appropriations.*

Year	OCRP Research Contributions	Additional Information and Hyperlinks
1997	Dr. Nicole Urban developed assays to measure HE4 and MSLN in serum; HE4 assay was licensed to Fujirebio Diagnostics, Inc., which partnered with Abbott, and was approved by the FDA as a new diagnostic test to monitor recurrence or progression of ovarian cancer.	
1998	Dr. Sundaram Ramakrishnan developed anginex, a potent anti-angiogenic and anticancer peptide (produced by ActiPep Biotechnology), and showed efficacy in combating ovarian cancer.	
1999	Dr. Richard Pietras developed and patented treatment of ovarian cancer with squalamine in combination with other anticancer agents/modalities (in Phase II clinical trials through Genaera Corporation).	
1999	Dr. Mary Daly published first resource book for high-risk women considering prophylactic oophorectomy, "Ovarian Cancer Risk-Reducing Surgery: A Decision-Making Resource."	<ul style="list-style-type: none"> <li>• <a href="#">OCRP Video Highlight</a></li> <li>• <a href="#">OCRP Research Highlight</a></li> </ul>
1999	Dr. Martin Cannon demonstrated that enhancing the CD8+ T cell response to ovarian cancer reduces the size of tumors in 75% of cases without surgery or chemotherapy.	
1999	Dr. Patricia Kruk found that inhibiting telomerase in cisplatin-resistant cells increases sensitivity to cisplatin treatment. Her research is among the first to indicate novel, extra-telomeric functions of telomerase.	<ul style="list-style-type: none"> <li>• <a href="#">OCRP Video Highlight</a></li> </ul>
2000	Dr. David Bowtell discovered that the Asn372His genotype of BRCA2 significantly increases the risk of ovarian cancer. Additionally, Dr. Bowtell identifies differences in epidemiological risk factors between ovarian, fallopian, and primary peritoneal cancer.	<ul style="list-style-type: none"> <li>• <a href="#">OCRP Video Highlight</a></li> </ul>
2000	Dr. David Bowtell discovered that the +331A allele of the progesterone receptor gene is significantly associated with protection against endometrioid ovarian cancer.	<ul style="list-style-type: none"> <li>• <a href="#">OCRP Video Highlight</a></li> </ul>
2001	Drs. Santo Nicosia and Jin Cheng discovered API-2/triciribine (Phase I clinical trials as VQD-002 are completed, now in Phase II clinical trials) as a putative inhibitor of Akt-activated cancers, which includes over 40% of ovarian tumors.	
2001	Dr. Andrew Berchuck established the International Ovarian Cancer Association Consortium.	
2002	Dr. Gordon Mills identified lysophosphatidic acids in serum and developed humanized monoclonal antibodies that have been shown to reduce tumor volume and metastasis in preclinical studies; this is now in Phase I clinical trials for the treatment of solid tumors.	
2003	Dr. Zhen Zhang, in collaboration with Vermillion, Inc., developed OVA1™, the first in vitro diagnostic multivariate index assay of proteomic biomarkers cleared by the FDA to help physicians identify ovarian cancer patients whose surgeries should be referred to a gynecologic oncologist.	

Year	OCRP Research Contributions	Additional Information and Hyperlinks
2003	Dr. Sandra Orsulic developed a novel mouse ovarian cancer model and mouse cell lines that lack the BRAC1 gene for studying the initiation and progression of hereditary ovarian cancer.	
2004	Dr. Igor Jurisica created OPHID/I2D, which are online databases of known and predicted protein-protein interactions, and NAViGaTOR, a software package for visualizing and analyzing PPI networks.	
2005	Dr. Janet Sawicki developed a targeted treatment using nanoparticles to deliver diphtheria toxin-encoding deoxyribonucleic acid to ovarian cancer cells, leaving healthy cells unaffected.	
2005	Dr. Xiaoyuan Chen developed multimeric arginine-glycine-aspartic acid peptides with high alpha-v-beta-3 integrin affinity for positron emission tomography (PET) imaging of ovarian cancer, received an exploratory Investigational New Drug approval, and initiated Phase 0 studies for the peptide tracer having the greatest tumor targeting efficacy in vivo.	
2005	Dr. Martin McIntosh discovered that MMP7 (matrix metalloproteinase 7) is elevated in serum up to 3 years prior to diagnosis of ovarian cancer.	
2005	Dr. George Coukos identified nine candidate proteins for specific expression in ovarian cancer tumor blood vessels that have potential use as therapy targets or imaging targets (patent pending for this set of markers). He also confirmed in a mouse model that the tumor endothelial marker 1 (TEM1) is a valid candidate for targeting cells in tumor blood vessels, and that the antibody MORAb-004 inhibits the establishment of tumor vasculature that expresses TEM1. This is an excellent example of public and private support of promising research as Morphotek is currently supporting multiple Phase 1 and Phase 2 trials testing this antibody (MORAb-004) in a variety of cancers.	
2006	Dr. Patricia Kruk demonstrated elevated urinary Bcl-2 as a biomarker in women at risk for ovarian cancer, and through a licensing agreement, Geopharma is developing a urinary detection device.	<ul style="list-style-type: none"> <li>• <a href="#">OCRP Video Highlight</a></li> </ul>
2006	Dr. Nouri Neamati developed substituted pyrimidyl guanidine derivatives having anticancer activity, particularly in ovarian cancer.	
2006	Dr. Stephen Howell showed that human Copper Transporter 1 (hCTR1) is necessary to transport platinum-based drugs into cells, and that resistance could be conferred by the cell degrading hCTR1. Multiple clinical trials are now treating with a proteasome inhibitor in conjunction with platinum-based therapy to boost efficacy.	
2006	Dr. Patricia Shaw established the Toronto Ovarian Cancer Research Network, a repository of prophylactic surgery specimens from BRCA mutation carriers with a database of BRCA mutation carrier and control group gene expression signatures.	
2007	Drs. Gillian Mitchell and David Bowtell identified BRCA1/2 mutations in 14% of the 1,001 samples from women with invasive nonmucinous ovarian tumors. Moreover, they observed that a high proportion of women carrying BRCA1/2 mutations did not have a significant family history of breast or ovarian cancer, thereby challenging the current practice of offering genetic testing only to women with a positive family history for those two cancers.	<ul style="list-style-type: none"> <li>• <a href="#">OCRP Video Highlight</a></li> </ul>

Year	OCRP Research Contributions	Additional Information and Hyperlinks
2007	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. This resulted in Australia changing the genetic testing guidelines in 2013 to include all women diagnosed with non-mucinous ovarian cancer under the age of 70.	<ul style="list-style-type: none"> <li>• <a href="#">OCRP Video Highlight</a></li> <li>• <a href="#">OCRP Research Highlight – 2012</a></li> <li>• <a href="#">OCRP Research Highlight – 2013</a></li> <li>• Cowin PA, George J, et al. 2012. LRP1B deletion in high-grade serous ovarian cancers is associated with acquired chemotherapy resistance to liposomal doxorubicin. <a href="#">Cancer Res</a> 72(16):4060-73.</li> <li>• Alsop K, Fereday S, et al. 2012. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: A report from the Australian Ovarian Cancer Study Group. <a href="#">J Clin Oncol</a> 30(21):2654-63.</li> </ul>
2008	Dr. Christine Walsh observed that a natural dietary phytochemical, indole-3-carbinol, sensitizes multiple ovarian cancer cell lines to bortezomib. This discovery has the potential to move bortezomib from the bench to the clinic as a treatment option for ovarian cancer.	
2008	Dr. Brad Nelson developed a new bioinformatics program for assembling high-throughput sequence data and querying for the presence of single nucleotide variants (SNVs) in ovarian cancer.	
2009	Dr. Fergus Couch identified a genetic locus associated with risk of ovarian cancer in BRCA1 mutation carriers, but not in BRCA2 mutation carriers or the general population. This was the first published report for a BRCA1-specific risk for ovarian cancer.	<ul style="list-style-type: none"> <li>• <a href="#">OCRP Research Highlight</a></li> <li>• Couch FJ, Wang X, et al. 2013. Genome-wide association study in BRCA1 mutation carriers identifies novel loci associated with breast and ovarian cancer risk. <a href="#">PLoS Genetics</a> 9(3): e1003212.</li> </ul>
2009	Dr. Eleanor Rogan found significantly higher levels of DNA-estrogen adducts in urine samples of women with ovarian cancer compared to controls, indicative of unbalanced estrogen metabolism, and potentially useful for non-invasive detection for risk and prevention.	
2009	Dr. Rugang Zhang observed that Wnt5a is expressed at lower levels in primary epithelial ovarian cancers; loss of Wnt5a correlates with a high cell proliferation index; and reconstituting Wnt5a in ovarian cancer cells causes cell senescence (irreversible cell growth arrest). These results suggest that targeting Wnt signaling is a novel strategy to induce senescence in epithelial ovarian cancer cells.	
2009	Dr. David Bowtell demonstrated that amplification of the 19q12 chromosomal locus is the most important chromosomal copy number change associated with primary treatment failure in ovarian cancer.	
2009	Dr. Kathryn Terry found that dominant tumors (ovarian origin) are more strongly associated with multi-parity, tubal ligation, and endometriosis, whereas non-dominant tumors (tubal origin) are more strongly associated with a family history of ovarian cancer and genetic variation in a telomere-associated protein, TERT.	<ul style="list-style-type: none"> <li>• <a href="#">OCRP Research Highlight</a></li> </ul>
2009	Dr. Tomas Walsh confirmed loss-of-function mutation in RAD51D gene predisposes women without BRCA1/2 mutations to ovarian cancer but not breast cancer. This information guides genetic testing kits for women in families with ovarian cancer with or without breast cancer.	

Year	OCRP Research Contributions	Additional Information and Hyperlinks
2010	Dr. Analisa DiFeo identified a microRNA biomarker (miR-181a) that shows promise in predicting treatment response in the most common form of ovarian cancer. miR-181a is one of the top expressing microRNAs in tumors from women who recurred within the first six months after treatment, and higher levels of miR-181a are seen in recurrent tumors compared to primary tumors.	
2010	Dr. Robert Kurman’s consortium developed and validated an inclusive scoring algorithm to assist pathologists in diagnosing Spatiotemporal Image Correlation Spectroscopy, the proposed precursor for most ovarian high-grade serous cancers.	
2010	Dr. James Cooper developed universal T-cells for immunotherapy that does not require patient-donated cells for their own therapy; in mouse models these effectively eliminate implanted human-derived ovarian cancer cells. This concurrently confirmed receptor tyrosine kinase-like orphan receptor-1 (ROR1) as an ovarian cancer-specific target for these cells.	
2010	Dr. Panagiotis Konstantinopoulos developed the BRCAness gene expression profile, which can identify tumors with the “BRCAness” phenotype (characterized by increased sensitivity to platinum analogues and poly ADP ribose polymerase [PARP] inhibitors as well as improved survival).	<ul style="list-style-type: none"> <li>• <a href="#">OCRP Research Highlight – 2013</a></li> <li>• <a href="#">OCRP Research Highlight – 2014</a></li> </ul>
2010	Dr. Kathryn Terry showed that women who take aspirin are at a reduced risk for non-dominant ovarian tumors, while women who take non-steroidal anti-inflammatory drugs (NSAIDs) other than aspirin are at a reduced risk for dominant and non-dominant ovarian tumors.	
2010	Dr. Martina Bazzaro demonstrated that combining bortezomib and vorinostat results in apoptotic morphology in ovarian cancer cells, but not in normal ovarian epithelial cells.	
2010	Dr. Rugang Zhang determined that Wnt5a, a non-canonical Wnt ligand, induces cellular senescence by activating histone repressor A/ promyelocytic leukemia senescence pathway. Wnt5a suppresses the growth of epithelial ovarian cancer, and loss of Wnt5a predicts a poor outcome in epithelial ovarian cancer patients.	
2011	Dr. Animesh Barua demonstrated that ultrasound imaging with VEGFR-2-targeted contrast agent improves the detection of ovarian tumors in hens compared to traditional ultrasound. Serum IL-16 and anti-NMP antibody levels were elevated prior to the development of a solid tumor mass in the ovary of the hen, suggesting that these could be biomarkers for early-stage ovarian cancer. This research represents an important step in the development of a novel approach for the diagnosis of early-stage ovarian cancer.	

Year	OCRP Research Contributions	Additional Information and Hyperlinks
2012	<p>Three Outcomes Consortium Development Awards were initiated to focus on discovering what distinguishes the small subset of ovarian cancer patients who become long-term survivors. This award represents a new approach that seeks to characterize the biology and genomics of tumors belonging to long-term survivors, as well as identifying lifestyle factors that affect carcinogenesis and therapeutic response in these patients. This initial Development Award enables the consortium to lay the groundwork for the research project, including proof of concept. Dr. Michael Birrer, Massachusetts General Hospital, and his research team plan to utilize the GOG database to discover what genomic features separate long-term survivors of ovarian cancer from other patients. Dr. Malcolm Pike, University of Southern California, and his consortium will analyze the tumors, treatments, and the patients themselves for the 20 percent of women diagnosed with high-grade serous ovarian cancer that survive past 10 years. Dr. Anil K. Sood, University of Texas MD Anderson Cancer Center, has assembled a consortium that will assess the power of biobehavioral and sociodemographic characteristics to predict long-term survival in women with serous ovarian cancer. They will also identify treatments and side effects that correlate with long-term survival.</p>	<ul style="list-style-type: none"> <li>• <a href="#">OCRP Research Highlight</a></li> </ul>
2012	<p>Dr. Paula T. Hammond identified a novel downstream signal effector in the p38 MAPK stress response pathway – activated in response to platinum chemotherapy – whose loss is synthetic lethal in ovarian cancer cells that lack functional p53. Her research team is engineering a series of lipid-like peptide co-polymers that self-assemble into nanoscale drug carriers that efficiently deliver small interfering RNA (siRNA) and platinum chemotherapeutics specifically to ovarian cancer cells. These nanotechnologies not only protect the siRNA from degradation during circulation, but also improve the fraction delivered to the tumor.</p>	<ul style="list-style-type: none"> <li>• <a href="#">OCRP Research Highlight</a></li> </ul>