

NEWSLETTER

2010



A Note from the Principal Investigator

Welcome to the 2010 edition of the Pacific Ovarian Cancer Research Consortium's (POCRC) newsletter, offered online only. We have just completed the first year of our 3rd 5-year period of SPORE funding from the National Cancer Institute (NCI), which means that we have been working diligently in the field for 11 years now. The POCRC has evolved from a small group of investigators working independently to a highly integrated interdisciplinary team of scientists with a focus on ovarian cancer. Over the years, new investigators have been attracted to the POCRC by its open and collaborative philosophy, and several new collaborations have been established in this funding period. I would like to take this opportunity to thank each of you for your support and to provide a brief update on the projects that are now underway.

Three inter-SPORE collaborations in which we took part during the previous funding period are being continued in the current funding period.

- First, the POCRC participated in a Phase I clinical trial evaluating the use of the anti-angiogenesis drug Avastin administered intravenously in combination with intraperitoneal administration of carboplatin and paclitaxel (the "Avastin Supplement"). Local and national accrual goals have been met for this study, so the trial is closed to further enrollment. The current goal is to complete treatment for all enrolled participants, collect follow up information on the participants' clinical status, and analyze the data collected. We are eager to learn the results of this trial because Avastin has performed well in similar studies.

- Next, the POCRC participated in the Proteomics Remission Monitoring Trial which involved study sites around the country and was overseen by the NCI. The trial was designed to develop a large repository of biological specimens and associated clinical data from ovarian cancer patients in their first remission following treatment with the goal of collecting enough specimens to identify and validate a biomarker panel to identify ovarian cancer recurrence as early as possible. Twenty participants were enrolled in Seattle, and Cedars Sinai Medical Center enrolled three. Over 115 were enrolled nationally. The study was closed to new enrollments last year, but we continued to follow previously enrolled participants through June of 2010. A Review Committee is now being formed to oversee the use of these precious samples and data in recurrence monitoring research studies.

- Finally, the POCRC has been participating in an inter-SPORE collaboration along with investigators from the Early Detection Research Network (EDRN) and the Prostate, Lung, Colon, and Ovarian Cancer Screening Trial (PLCO) entitled, "Phase III Validation of a Consensus Panel of Ovarian Cancer Markers". The goal of this collaboration is to identify markers that may be used in combination to detect ovarian cancer in its early stages when it most curable. We and the other participating investigators received the PLCO proximate sera collected from study participants prior to their ovarian cancer diagnosis along with sera from matching controls. Thirty-five biomarkers were measured by five different sites, with some markers being measured at multiple sites. As expected, CA125 was the top-performing marker; HE4, a marker originally identified as important to ovarian cancer by POCRC investigators, was



Nicole Urban, ScD,
Principal Investigator

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the next best performing marker. We also received PLCO's serial CA125II measures and ultrasound results from the ovarian cancer cases. We used those data to get a baseline performance estimate of the PLCO multimodal strategy and are in the process of publishing our results. Next we will receive serial serum samples from the same PLCO participants and will measure our best-performing markers in them to determine whether the use of the parametric empirical Bayes (PEB) longitudinal algorithm developed during a previous SPORE funding period improves markers' ability to detect ovarian cancer early.

We're very pleased that City of Hope (COH) in Duarte, CA and Stanford University Medical Center in Palo Alto, CA have joined the FHCRC and Cedars Sinai Medical Center (CSMC) to conduct the Phase I clinical trial in Project 1 (The Novel Markers Trial, <http://www.pocrc.org/project-1.html>). Drs. Pam Paley and Charles Drescher lead the clinical and coordinating work respectively at FHCRC, and Dr. Beth Karlan leads the work at CSMC. These long-time collaborators are joined for the Novel Markers Trial by three new POCRC investigators. Dr. Melanie Palomares is responsible for study implementation at COH while Drs. Jonathan Berek and Allison Kurion lead the efforts at Stanford. An update on the Novel Markers Trial is included in this newsletter.

Another Stanford investigator, Dr. Sanjiv (Sam) Gambhir, is working with Dr. Charles Drescher on Project 2 (<http://www.pocrc.org/project-2.html>). Dr. Gambhir brings a wealth of knowledge about radiographic imaging to bear on the early detection effort and is a welcome addition to the POCRC. This project will include a Phase I clinical trial to evaluate the use of targeted microbubbles to image early stage ovarian cancer in women undergoing sonography.

Project 3 (<http://www.pocrc.org/project-3.html>) is led by Dr. Muneesh Tewari who previously received POCRC pilot awards through Career Development Program (CDP) and Developmental Research Program (DRP) funding. He successfully turned his pilot work into a full scale translational research project dealing with miRNA expression and ovarian cancer prognosis.

Investigators new to the POCRC are responsible for Project 4 (<http://www.pocrc.org/project-4.html>). Dr. Toshiyasu Taniguchi (FHCRC) and Dr. Elizabeth Swisher (University of Washington Medical Center) both had benefitted in the past from POCRC cores, and we are pleased that they have joined us with their efforts to evaluate the role in chemoresistance of reversion of mutated BRCA genes to wild type. A feature article on this team and their project is included in this newsletter.

Dr. Nora Disis of the University of Washington is the Principal Investigator for Project 5 (<http://www.pocrc.org/project-5.html>). Dr. Disis returns to the POCRC after taking a hiatus during the previous funding period. She and her team, including Drs. Ron Swensen and Lupe

Salazar, will conduct a Phase I clinical trial to test an ovarian cancer vaccine. We're thrilled to have Dr. Disis leading our efforts in immunotherapy once again.

Brand new to the POCRC is Dr. Carla Grandori, recipient of the most recently awarded DRP funding. Dr. Grandori and her post doctoral fellow, Dr. Masafumi Toyoshima, bring a new perspective and important resources to the POCRC. More information about their project is included in this newsletter.

Finally, the POCRC welcomes its newest advocate, Janet Fleck. Advocates are at the heart of what we do; they provide invaluable insight to our research. We have included an interview with Janet in this newsletter so you may get to know her and her advocate's heart.

Thank you all for your continued dedication and commitment to the POCRC!

Sincerely,



Nicole Urban, ScD.



Update on SPORE Project 1, Novel Markers Trial

The newly funded ovarian SPORE—The Pacific Ovarian Cancer Research Consortium (POCRC)—includes an ovarian cancer screening study called the Novel Markers Trial (NMT, <http://www.pocrc.org/project-1.html>). The trial is currently enrolling participants at Swedish Medical Center in Washington State, and Cedars-Sinai Medical Center, City of Hope and Stanford University Medical Center in California. NMT is an important step in a larger research effort to develop a screening strategy for the early detection of epithelial ovarian cancer (EOC). Our primary goal is to compare the safety and feasibility of two different screening strategies utilizing the biomarkers CA125 and HE4. Researchers will compare rates of protocol-indicated surgical procedures performed per cancer detected between the two strategies. They will also compare compliance with primary screens, secondary screens, and surgical referrals between the two screening strategies. Finally, they will look at how each strategy impacts quality of life by assessing cancer worry. If promising new markers are discovered during the study period, those markers will be evaluated for their potential contribution to the screening strategy.

The POCRC site at Fred Hutchinson Cancer Research Center serves as the coordinating center for NMT and is supported through the efforts of the four POCRC Cores. The Leadership Core (<http://www.pocrc.org/leadership-core.html>) provides oversight and meeting support to the project. Because the NMT is a collaborative effort that currently involves investigators at the Fred Hutchinson Cancer Research Center (FHCRC) as well as investigators and staff at four clinical sites in Washington and California, a great deal of coordination and communication are required to ensure that the trial runs smoothly at all sites.

Both the Canary Foundation and the Marsha Rivkin Center for Ovarian Cancer Research are providing substantial supplemental funding to make the NMT possible. In addition, Abbott Laboratories is generously providing free clinical CA125 and HE4 kits to run on the Abbott ARCHITECT®i1000SR® immunochemistry analyzer that the Canary Foundation purchased for this trial. The ARCHITECT is located at the Marsha Rivkin Center. Specimen Core (<http://www.pocrc.org/specimen-core.html>) staff members have been trained in the instrument's operation and use it weekly to measure CA125 and HE4 in all NMT participants' serum after they are enrolled through the efforts of the Clinical Core (<http://www.pocrc.org/clinical-core.html>). All study sites use the same specimen collection/processing protocol and send samples for marker measurement to the FHCRC to ensure that all specimens are measured on the same platform by the same technicians, thereby providing consistency to the results.



Abbott ARCHITECT i1000 located at the Marsha Rivkin Center for Ovarian Cancer Research

Informatics Core (<http://www.pocrc.org/bio-core.html>) staff members at FHCRC have worked closely with investigators and study staff at all sites to develop a NMT Tracking System. The system includes a computerized eligibility algorithm that uses the information that women provide on an eligibility screening questionnaire to determine whether or not each woman meets trial eligibility criteria. The system is used to track participants who have enrolled in the study and shows exactly where each participant is in the study process, prompting staff when it is time to send screening reminder letters or to perform some other action. A web-based platform was developed to facilitate access across remote sites. This was no small feat given the fact that staff members at the FHCRC coordinating center are not permitted to see personal identifying information for participants at some of the other sites. In addition, a Results Tracking System was designed to run the PEB longitudinal algorithm to determine whether or not CA125 and HE4 results are elevated sufficiently to warrant calling the screen positive. The Results Tracking System forwards results to the NMT Tracking System so that the appropriate screening results letter(s) can be generated by this sophisticated system.

Recruitment Update

The first participant was enrolled in February, 2010. As of August 20, 2010, a total of 231 women have enrolled in the trial.

Spotlight—Project 4

Toshiyasu Taniguchi, MD, PhD
and Elizabeth Swisher, MD

We are very pleased to have Drs. Toshi Taniguchi and Elizabeth Swisher join the POCRC this funding period with their SPORE Project 4: Clinical implication of the acquisition of BRCA1/2 function in BRCA1/2-deficient ovarian carcinoma. Both investigators have worked before with POCRC patient specimens through the clinical and specimen cores, but this is the first time either has led a SPORE project.

Dr. Taniguchi joined the Hutchinson Center in 2004. In 2009 he received the prestigious honor of being appointed as a Howard Hughes Medical Institute Early Career Scientist. He brings to the SPORE a wealth of experience in the areas of cell cycle checkpoints and DNA repair. He has worked extensively to understand the Fanconi Anemia-BRCA pathway and its relationship to chemosensitivity of human cancer.

Dr. Swisher joined the University of Washington's Department of Obstetrics & Gynecology in 1999. As a UW gynecologic oncology surgeon, she actively participates in clinical trials for women with gynecologic malignancies and directs the Breast and Ovarian Cancer Prevention Program. Her research interests are in cancer genetics and in understanding the origin, prevention, and treatment of hereditary and nonhereditary ovarian cancers. She is widely published on these topics and has been collaborating with Dr. Taniguchi for several years as well as with Mary-Claire King PhD, a renowned geneticist.

A brief summary of SPORE Project 4 may be found here: <http://www.pocrc.org/project-4.html>. The study's primary translational goal is to develop better predictors of platinum response in recurrent hereditary ovarian carcinomas to allow more accurate prediction of treatment response for women with recurrent disease and to develop therapeutic strategies to overcome platinum resistance.

The study's specific aims are:

Specific Aim 1: Assess the contribution to platinum resistance of secondary mutations of BRCA1/2 that restore DNA repair function in BRCA1/2-mutated ovarian carcinomas.

Aim 1A: Determine whether the occurrence of secondary mutations of *BRCA1/2* that restore DNA repair function correlates with clinical outcomes of **recurrent** ovarian carcinomas in women with *BRCA1/2* germline mutations.

Aim 1B: Determine whether the occurrence of secondary mutations of *BRCA1/2* that restore DNA repair function correlates with clinical outcomes of **primary** ovarian carcinomas in women with *BRCA1/2* mutations.

Specific Aim 2: Determine whether restoration of BRCA1 expression contributes to acquired platinum resistance of sporadic ovarian carcinomas with initially low BRCA1 expression.

Aim 2A: Determine whether restoration of BRCA1 protein expression occurs in clinical specimens obtained after chemotherapy compared to paired neoplasms from the same patients obtained before chemotherapy and assess whether restoration of BRCA1 expression correlates with clinical outcomes and response to chemotherapy.

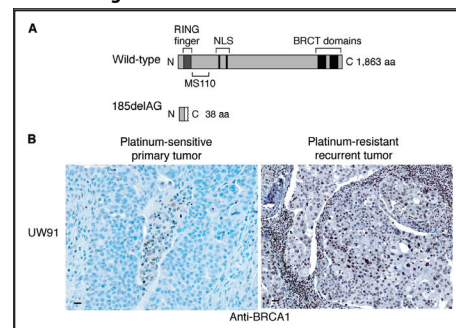
Aim 2B: Determine if restoration of BRCA1 expression and function occurs in ovarian cancer cells with reduced BRCA1 expression after *in vitro* selection in the presence of cisplatin and assess mechanisms of that restoration.

Studies to date have focused on Specific Aim 1. Over 60 primary ovarian carcinoma samples and over 40 recurrent ovarian carcinoma samples in women with *BRCA1/2* mutations have been studied. Pure tumor cell populations were obtained from the tissues using laser-capture microdissection, and DNA was extracted. Then, *BRCA1* or *BRCA2* was sequenced for secondary *BRCA1/2* mutations which restore functional *BRCA1/2* reading frame. Analyses revealed that:

- 1) Secondary *BRCA1/2* mutations were much more frequently observed in recurrent carcinomas than in primary carcinomas.
- 2) A previous diagnosis of breast cancer increased the likelihood of identifying a secondary mutation in the ovarian carcinoma.
- 3) The presence of a secondary *BRCA1/2* mutation predicted resistance to platinum chemotherapy.

The data generated to date support the hypothesis that secondary mutations that restore the DNA repair function of *BRCA1/2* lead to tumor resistance to platinum based chemotherapy, and preliminarily suggest that tumors with secondary mutations should be treated with other agents. Additional samples will be evaluated in the coming years to expand these findings. In addition, work on Specific Aim 2 will begin in the coming year.

BRCA1 protein expression is restored in recurrent ovarian tumors with genetic reversion of BRCA1 mutation.



Swisher E M et al. Cancer Res 2008;68:2581-2586
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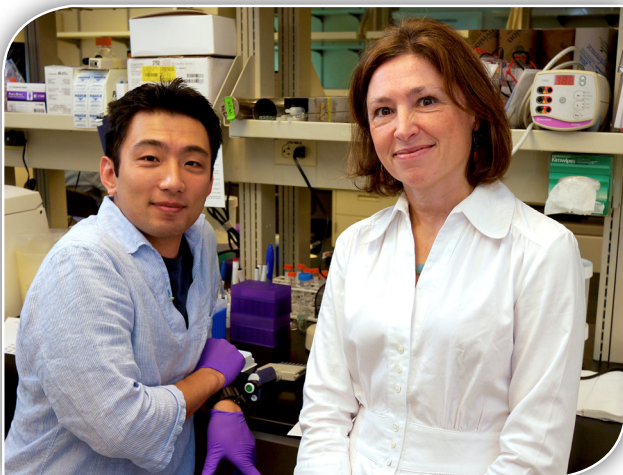
Spotlight—2010 Developmental Research Program Pilot Funds Recipient

Carla Grandori, MD, PhD

February, 2010 brought with it a new Request for Applications (RFA) for POCRC Developmental Research Program (DRP) funds. Six proposals were received in April, and all were reviewed quite favorably. The top-scoring proposal was submitted by Dr. Carla Grandori, an Affiliate Investigator in FHCRC's Human Biology Division; this proposal was funded beginning July 1st, 2010. Dr. Grandori has a joint appointment at the University of Washington's Institute of Stem Cell and Regenerative Medicine where she oversees the operation of the Quellos High Throughput Screening Core. Dr. Grandori plans to apply her experience in cancer biology with high throughput technology to carry out functional genomic screens aimed at identifying new therapeutic approaches for ovarian cancer. This goal is illustrated by the title of Dr. Grandori's DRP Project: "Identification of Targeted Therapies for Ovarian Cancer by Functional Genomics".

Dr. Masafumi Toyoshima, a post-doctoral fellow in Dr. Grandori's laboratory, has played an essential role in the design of this project and in carrying out preliminary experiments to validate the approach. Dr. Toyoshima has a strong interest in ovarian cancer due to his clinical experience as a trained gynecologic oncologist. He is also an accomplished researcher with experience in ovarian cancer models, functional genomics and molecular biology. Dr. Toyoshima is a recent recipient of a Marsha Rivkin Center for Ovarian Cancer Research Scientific Scholar Award.

The first Aim of this proposal focuses on identifying drug targets for *MYC* driven ovarian cancers. Alterations of *MYC* family oncogenes have been observed in many human cancers and are generally associated with poor prognosis. Only recently its overexpression and/or gene amplification has also been detected in ovarian cancer with an incidence estimated to be >60%.



Because the *MYC* family of oncogenes encode for transcription factors with an essential role in proliferating tissues, identifying small molecule inhibitors is difficult and their use could have catastrophic consequences for the organism. Thus, Dr. Grandori and Dr. Toyoshima have elected to utilize functional genomic screening to identify potentially non-essential genes exhibiting "synthetic lethality" in the context of aberrantly high *MYC*. Their recent work has indicated that such genes exist and that they represent effective targets for therapy. The second Aim will utilize functional genomics to identify therapeutic targets for chemoresistant ovarian cancer cells. As the problem of chemoresistance is a major determinant of treatment failure in ovarian cancer, progress in this area will be of great relevance to the field.

Finally, a key collaborator of this project is Dr. Toshi Taniguchi, who is also the PI of SPORE Project 4. Dr. Taniguchi will provide to Dr. Grandori's team his extensive expertise in mechanisms of ovarian cancer drug resistance and DNA repair pathways. The proximity of Dr. Taniguchi's laboratory to Dr. Grandori in the Human Biology Division will greatly facilitate the exchange of information and close collaboration on these projects.

Together this multi-disciplinary team of Grandori and Toyoshima brings new technologies to the POCRC with a dedication to translational ovarian cancer research. These outstanding investigators have the potential to make a novel and substantial impact in the field.

Interview with POCRC Advocate Janet Fleck

We would like to introduce you to our newest POCRC Advocate, Janet Fleck. Janet kindly answered some questions recently to help us learn more about her.

1. Please tell us a bit about yourself.

I am the 2nd born of 7 children (5 boys, 2 girls). I was born in Iowa and moved to Rochester then Albany, NY. I met Dennis in Albany, and after a short courtship we married and moved to the Phoenix, Arizona area where our two children were eventually born! We moved to the Seattle area in 1981 and are still in the same house. My son lives in Denver with his wife, and my daughter lives in the Berkeley, CA area where she works for a biotech company.

I am an ovarian cancer survivor but that is such a small part of who I am. I graduated from the University of Washington with a degree in Anthropology focusing on the biological aspects. I was heavily involved with PTSA, Bellevue Children's Theater, Soccer mom, all the things moms did when their children were young. Now, I'm on our community board and am involved with Team Survivor Northwest (TSNW) as both a member—

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trying everything they have to offer—and as a member of the TSNW Volunteer Committee. My cycle club sponsors the Cycle the Wave event in September that raises money for Eastside Domestic Violence Program. I am committee chair for “The Holiday Giving Tree” at my church that collects holiday gifts for both troubled youth and foster children. And now I am also involved with the POCRC.

My hobbies are cycling (I love my bike!!!) and running. Prior to a recent injury I was training for both the Rock N Roll 1/2 Marathon and the Trek Triathlon. I completed my first triathlon last summer. What a rush! Now, I’m just doing 5K’s until I can work up to doing the 1/2 marathon and tri’s again.

Currently I’m doing yoga, water aerobics and walking to recover. I love reading, sewing and hiking among other activities.

Job wise, I am currently working at the Bellevue Aquatic Center—which started as part of my recovery from the cancer- oh... that cancer thing... Ovarian Cancer—Stage I, grade I. As you can see... it really hasn’t defined me but it has brought me to where I am.

2. How did you hear about the POCRC advocacy program?

I found out about the advocacy program after hearing Nicole Urban and others on a panel speak at a Seattle #4 Rotary luncheon. I contacted her about potentially helping, explaining I would love to be involved. She suggested the advocacy program.

3. What has been your experience in your role as a POCRC advocate to date?

I feel I’m still learning about the program and how it works but am feeling so much more comfortable as to what it is and what is involved. I now attend Scientific Program Committee meetings where I get to hear about the research various investigators are conducting. I’ve also been able to participate in the review process for the Developmental Research Program. The research presented is fascinating, and I wish the group had the funds to support all of the proposals. I feel that it is within their ability to learn as much about the cancer as possible and it’s with both the successes and failures that the answer will come to early detection or any potential for a cure (if it were only so easy). It has always been obvious to me that it’s only through donations, grants and willing patients for the trials that there will be success.

4. Do you have any suggestions for others who might want to get involved?

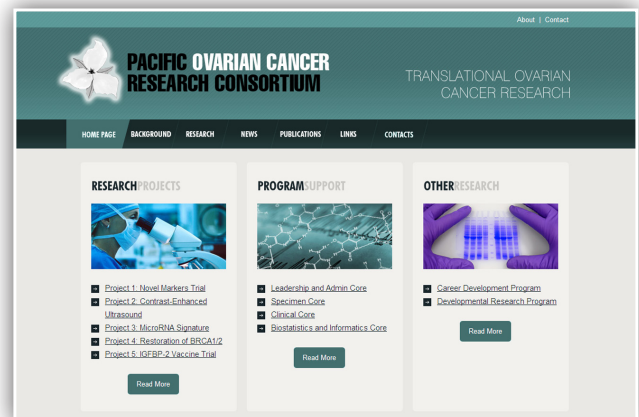
The best solution is to contact a person who knows where help is needed and how to put the advocate to work. Promoting POCRC to groups and getting the message out about what the organization is and

does is imperative. For me it was a Rotary meeting. Today at the Swedish Summer Run there was a table set up for POCRC! It was exciting to see! What a great way to promote this group and potentially find new volunteers. What I would like personally is a simple explanation or ‘party line’ to tell everyone what POCRC is, and what people can do.

More simply... for someone who wants to be involved... ASK where you can be of help. And for people already involved... spread the word!

For More Information

For more information about the POCRC Advocacy Program you may contact the POCRC’s Research Nurse, Shirley Gough, at sgough@fhcrc.org.



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