Queen of Hearts Foundation for Ovarian Cancer Research
March 10, 2011

Review of the Drs. Brewster/Burger Research

Your generous support of Drs. Brewster and Burger was critically important to their research and ensuing publications. A complete list of their ovarian cancer-related publications and research to which your generous support contributed to, at least in part, is in the Appendix.

Review of Dr. Burger's Research

Specifically, your support of Dr. Burger provided the resources that led to the publication of nineteen research articles in leading journals such as *Gynecologic Oncology, Cancer*, *Cancer Research*, the *Journal of Clinical Oncology*, and the *New England Journal of Medicine*. Dr. Burger made excellent use of your support by engaging in a variety of research areas related to ovarian cancer. One of his specific areas of focus was the identification of ways to more effectively treat women with ovarian cancer by discovering new chemotherapy treatment combinations and predicting which drugs certain women would or would not respond to. For example, one of his research projects, conducted in conjunction with UC Irvine colleague Dr. John Fruehauf, studied differences in responsiveness to chemotherapy according to the different types of ovarian cancer (Burger [3], Fruehauf [1]). This is the largest study of its type to date and examined over 5,000 tumors from ovarian cancer patients all over the United States. The results have helped to shape the clinical management of women with ovarian cancer, as Drs. Burger and Fruehauf identified important differences for the chances of chemotherapy response among different types of ovarian cancer but also discovered novel changes in expression of key molecular markers.

Another project conducted by Dr. Burger reported the UC Irvine experience treating women with the most difficult to treat subset of women with ovarian cancer – those with disease that is resistant to platinum-based chemotherapy (Burger [4]). In this study, Dr. Burger was one of the first investigators to describe an increased likelihood of response and improved survival for this group of patients by using a novel treatment combination of the drugs cisplatin and gemcitabine. This study opened up a new treatment option and provided the hope for extended survival for a group of ovarian cancer patients previously without many options. Continuing along this line of investigation, Dr. Burger also contributed to important basic science work, along with his more clinically focused pursuits, directly supported by the Queen of Hearts Foundation support. For example, Dr. Burger's laboratory made substantial contributions to a study that examined the molecular blockade of Epidermal Growth Factor receptors (EGFR) as it pertains to chemotherapy resistance to cisplatin in ovarian cancer patients (Burger [7]). This particular study utilized a very intricate in vivo rat model and identified EGFR blockade as a potential therapeutic target for women with platinum-resistant ovarian cancer. This seminal work led to actual clinical use of EGFR blockade in ovarian cancer patients and is now one of the more promising treatment strategies moving into the era of molecularly targeted therapies in addition to or instead of more traditional chemotherapy treatment.

In addition to directly supporting Dr. Burger's clinical and laboratory work, as described above, the funding by the Queen of Hearts Foundation provided critical salary support for Dr. Burger that allowed him to devote a portion of his time to ground-breaking studies by the Gynecologic Oncology Group (GOG), the world's premier cooperative group conducting clinical trials for women with gynecologic cancer. As a result, Dr. Burger has made contributions to ovarian cancer science and literature fields that have changed the way that ovarian cancer is treated in the United States and around the world. There

are two lines of investigation that have been of particular distinction. First, Dr. Burger was a key investigator in the practice-changing GOG studies that showed that the use of intra-peritoneal chemotherapy for women with advanced-stage ovarian cancer improved survival time by more than 20% (Burger [8, 9]). The second line of investigation has been the use of Bevacizumab, a novel blood vessel growth-inhibitor, for women with ovarian cancer. Dr. Burger is one of the leading researchers on the use of this drug for ovarian cancer, and much of his work in this area was performed while he was at UC Irvine (Burger [10, 11, 12]). As a result of this work conducted by Dr. Burger, and indirectly supported by the Queen of Hearts Foundation providing him protected research time, Bevacizumab is the the first biological agent (non-traditional chemotherapy) to be incorporated into the front-line treatment program for women with ovarian cancer. This truly has been paradigm-changing scientific work.

Review of Dr. Brewster's Research

Your support of Dr. Brewster led the publication of twelve research articles in leading journals such as the *American Journal of Clinical Oncology*, *Cancer Epidemiology, Biomarkers, and Prevention*, the *British Journal of Cancer*, and *Gynecologic Oncology*. The Queen of Hearts Foundation donation was used to support Dr. Brewster's research focused the genetics and epidemiology of ovarian cancer and patterns of healthcare delivery both directly and in the form of protected research time. As a result of this support, Dr. Brewster made substantial contributions to the field of ovarian cancer research and generated twelve publications and other scientific projects. Specifically, Dr. Brewster utilized a portion of the Queen of Hearts support for laboratory work and specimen processing on several important cancer genetic studies that have advanced our knowledge about why ovarian cancer occurs and which women are at the greatest risk (Brewster [4, 5, 6, 8, 9, 10, 11]). Through the Queen of Hearts support, Dr. Brewster was able to participate and contribute samples to the largest worldwide consortium of ovarian cancer genetic epidemiology researchers, the Ovarian Cancer Association Consortium. One study in particular conducted by this group, and Dr. Brewster, identified a key genetic pathway predisposing some women to develop ovarian cancer that had not been previously known (Brewster [8]).

Dr. Brewster also made important contributions to the understanding of the link between a specific type of ovarian cancer – tumor of low malignant potential – and the risk of developing a subsequent breast cancer (Brewster [3]). This work, for which the Queen of Hearts Foundation support provided her protected time for research, has had an important impact on the way we counsel and screen patients with this type of ovarian cancer during their cancer surveillance program. Another seminal paper by Dr. Brewster studied the impact of socioeconomic factors on the way that women with ovarian cancer are cared for (Brewster [7]). This study determined that women of lower socioeconomic status are less likely to receive standard treatment and has been an influential piece of the puzzle as healthcare administrators and policy-makers struggle to make sure that all women with ovarian cancer receive the best chance for long-term survival and cure.

Research Review: Summary and Next Steps

In summary, the above body of work is a wonderful example of how a partnership with an organization like the Queen of Hearts can lead to advances in the fight against ovarian cancer and help the courageous women that must face this disease every day.

In addition to the research detailed above, there are funds remaining from your initial gifts that I propose to use to continue to support research examining disparities in ovarian cancer care and the comparative effectiveness of different treatment strategies for women with advanced-stage disease. I am currently working on two specific projects that should reach publication within the next 6 months:

- Contemporary Surgical Treatment Paradigms for Stage IIIC Epithelial Ovarian Cancer and the Impact of Complete Tumor Resection.
- Disparities in Ovarian Cancer Treatment and Outcome: the Impact of Care at a Tertiary Referral Center.

I believe that this research is directly related to the vision of the Queen of Hearts, and as such I would like to recognize your contributions in the ensuing publications. In fact, in recognition of our partnership, I would propose that every ovarian cancer research paper and publication submitted by the Division of Gynecologic Oncology would include a byline recognizing the philanthropic support, and partnership, of the Queen of Hearts Foundation for Ovarian Cancer Research.

APPENDIX
Publications and Other Research Activities

Dr. Burger	Period	Type
1. Activity of bevacizumab (rhuMAB VEGF) in advanced refractory epithelial ovarian cancer. Gynecol Oncol 96, (3) 902-5.	2004	Publication
2. Association between serum levels of soluble tumor necrosis factor receptors/CA125 and progression in patients with epithelial ovarian cancer: a Gynecologic Oncology Group (GOG) study. Cancer 101, (1) 106-15.	2004	Publication
3. In vitro chemoresistance and biomarker profiles are unique for histologic subtypes of epithelial ovarian cancer. Gynecol Oncol 92, 160-166.	2004	Publication
4. Gemcitabine and cisplatin chemotherapy is an active combination in the treatment of platinum-resistant ovarian and peritoneal carcinoma. Invest New Drugs 22, 475-80.	2004	Publication
5. Conservation of in vitro drug resistance patterns in epithelial ovarian carcinoma. Gynecol Oncol 98(3), 360-8.	2005	Publication
6. Implications of second-look laparotomy in the context of optimally resected stage III ovarian cancer, A non-randomized comparison using an explanatory analysis: A Gynecologic Oncology Group Study. Gynecol Oncol 99(1), 71-9.	2005	Publication
7. Suppression of ovarian cancer cell tumorigenicity and evasion of cisplatin resistance using a truncated epidermal growth factor receptor in a rat model. Cancer Res 65, (8) 3243-8.	2005	Publication
8. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 354, 34-43.	2006	Publication
9. Intraperitoneal catheter outcomes in a phase III trial intravenous versus intraperitoneal chemotherapy in optimal stage III ovarian and primary peritoneal cancer: a Gynecologic Oncology Group Study. Gynecol Oncol 100(1), 27-32.	2006	Publication
10. Salvage bevacizumab (rhuMAB VEGF)-based therapy after multiple prior cytotoxic regimens in advanced refractory epithelial ovarian cancer. Gynecol Oncol 102, 140-4.	2006	Publication
11. Experience with bevacizumab in the management of epithelial ovarian cancer. J Clin Oncol Jul;25(20):2902-8.	2007	Publication
12. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. J Clin Oncol 25, 5165-71.	2007	Publication
13. ECA1 is a secreted protein expressed in a subset of ovarian and colorectal carcinomas with Wnt/ß–catenin pathway activation. Bahman Saffari, Michael F. Press, Xu Huang, Basmina Parmakhtiar, and Robert A. Burger. AACR Meeting Abstracts, Mar 2004: #636.	2004	Meeting Abstract
14. Conditioned media from ECA1-transfected HEK 293 cells enhances cellular proliferation in vitro. Bahman Saffari, Basmina Parmakhtiar, John Fruehauf, and Robert Burger. AACR Meeting Abstracts, Apr 2005: 1298 - 1299.	2005	Meeting Abstract
15. Prognostic Significance of Endometrioid Carcinoma 1 (ECA1): Enhanced Cancer Cell Proliferation. Basmina Parmakhtiar, Bahman Saffari, John P. Fruehauf, and Robert A. Burger. AACR Meeting Abstracts, Apr 2006: # 628.	2006	Meeting Abstract
16. API36576-UCI 04-12 Phase II Randomized Double-Blind, Placebo-Controlled, Parallel-Group Trial of the Clinical Activity and Safety of Two Dose Levels of Subcutaneous Angstrom A6 in Patients with Asymptomatic CA 125 Progression of Epithelial Ovarian Cancer	2004-2005	Sponsored Project/Clinical Trial
17. GCF34708-The Role of ECA1 in Ovarian Carcinogenesis and Potential Utility as a Serum Marker	2004	Sponsored Project

18. GOG-170-F-A Phase II Evaluation of BAY 43-9006 (NCI-Supplied Agent, NSC #724772, IND #69-896) in the Treatment of Persistent or Recurrent Epithelial Ovarian or Primary Peritoneal Carcinoma	2004-2007	Clinical Trial
19. UCI-05-07-An Open-label Multicenter Randomized Phase III Study Comparing the Combination of Doxil/Caelyx and Yondelis with Doxil/Caelyx Alone in Subjects with Advanced Relapsed Ovarian Cancer**	2005-2007	Clinical Trial

Dr. Fruehauf	**Period**	**Type**
1. Differential in vitro drug response for histological subsets of ovarian carcinoma. Gynecol Oncol 92, 160-166.	2004	Publication
2. Conservation of in vitro drug resistance patterns in epithelial ovarian carcinoma. Gynecol Oncol 98(3), 360-8.	2005	Publication
3. The Relationship Of Molecular Markers Of P53 Function And Angiogenesis To Prognosis Of Stage I Epithelial Ovarian Cancer. Clin Cancer Res 11, 3733-3742.	2005	Publication
4. Predictive and prognostic angiogenic markers in a gynecologic oncology group phase II trial of bevacizumab in recurrent and persistent ovarian or peritoneal cancer. Gynecol Oncol 119, 484-90.	2010	Publication
5. Targeted therapy in ovarian cancer. J Oncol 2010, 740472.	2010	Publication
6. 104864/547-UCI 099-25R: Topotecan Plus Cisplatin Followed by Paclitaxel for Stage III and IV Epithelial Ovarian and Primary Peritoneal Cancer	2005 - 2007	Sponsored Project/ Clinical Trial
7. HYN107716-UCI 99-25-R: Oral Topotecan, Utilication of a Metronomic Dosing Schedule to Treat Recurrent Ovarian Cancer	2008-2010	Sponsored Project/ Clinical Trial
8. RSA1000950-Synergistic Action of Topotecan with Imatinib (Gleevac) on Ovarian Cancer Cell Lines	2004	Sponsored Project

Dr. Brewster	**Period**	**Type**
1. Commentary: Temporal trends in ovarian cancer incidence across Europe. Nat Clin Pract Oncol Jun 2(6), 3.	2005	Publication
2. Could a pelvic and abdominal symptom index assist in early detection of ovarian cancer? Nat Clin Pract Oncol 4, 338-9.	2007	Publication
3. Epithelial Ovarian Cancer and LMP Tumors Associated with a Lower Incidence of Second Primary Breast Cancer. Am J Clin Oncol30(1), 1-7	2007	Publication
4. Polymorphism in the IL18 Gene and Epithelial Ovarian Cancer in Non-Hispanic White Women. Cancer Epidemiol Biomarkers Prev 17, 3567-3572.	2008	Publication
5. Association between invasive ovarian cancer susceptibility and 11 best candidate SNPs from breast cancer genome-wide association study. Hum Mol Genet 18:12, 2297-304.	2009	Publication
6. A genome-wide association study identifies a new ovarian cancer susceptibility locus on 9p22-2. Nat Genet 41, 996-1000.	2009	Publication
7. Socioeconomic factors may contribute to neoadjuvant chemotherapy use in metastatic epithelial ovarian carcinoma. Gynecol Oncol 115(3), 339-42.	2009	Publication

8. Validating genetic risk associations for ovarian cancer through the international Ovarian Cancer Association Consortium. Br J Cancer 100, 412-20.	2009	Publication
9. A genome-wide association study identifies susceptibility loci for ovarian cancer at 2q31 and 8q24. Nat Genet 42, 874-9.	2010	Publication
10. Common variants at 19p13 are associated with susceptibility to ovarian cancer. Nat Genet 42, 880-4.	2010	Publication
11. ESR1/SYNE1 polymorphism and invasive epithelial ovarian cancer risk: an Ovarian Cancer Association Consortium study. Cancer Epidemiol Biomarkers Prev 19, 245-50.	2010	Publication
12. Ortho Bio Tech, OBT34325-Doxil Consolidation Therapy in Women with Advanced Stage Ovarian Cancer	2004-2006	Sponsored Project