NORTHWEST
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Program & Abstracts

SEPTEMBER 25, 2019

ORIN SMITH AUDITORIUM | UW SLU | SEATTLE, WA

RIVKINCENTER

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Program

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Moderator **Rosana Risques, PhD** (2017 Pape Family Pilot Study Award; 2019 Rivkin Bridge Funding Award)

8:40am – 8:55am *Characterization of TP53 mutations in Pap test DNA of women with and without serous ovarian cancer*
Rosana Risques, PhD, University of Washington

8:55am – 9:10am *The effect of OCP use on the incidence of pre-cancerous p53 lesions in fallopian tube fimbria*
Kendall Greening, MSc, BC Cancer Research Centre

9:10am – 9:25am *Clinical tissue proteomics identifies new mesonephric carcinoma biomarkers*
Evan Gibbard, University of British Columbia

9:25am – 9:40am *Ethnic disparity in detection of ovarian malignancy*
Charles Dunton, MD, ASPiRA Labs

9:40am – 10:10am **Coffee Break**

SESSION II: CANCER MECHANISMS

Moderator **Bo Yu, MD** (2017 Cookie Laughlin Bridge Funding Award)

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Joyce Zhang, BC Cancer Research Centre

10:25am – 10:40am *Targeted next-generation sequencing identifies mutations in epigenetic regulators in a large cohort of adult-type granulosa cell tumors*
Jessica Pilsworth, University of British Columbia

10:40am – 10:55am *Single cell RNA sequencing of normal endometrial organoids reveals prognostic markers in gynecologic tumors*
Dawn Cochrane, PhD, BC Cancer Research Centre

10:55am – 11:00am **Keynote Introduction by Mark Carey, MD**

11:00am – 12:00pm **Keynote Address**
Defining the trajectory of ovarian cancer from early tubal precursors
Ronny Drapkin, MD/PhD, University of Pennsylvania

12:00pm – 1:00pm **Lunch** (provided)

12:00pm – 1:00pm **Trainee Lunch with Keynote Speaker**

SESSION III: MANAGEMENT AND RESOURCES

Moderator **Robyn Andersen, PhD** (2017 Pilot Study Award)

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Robyn Andersen, PhD, Fred Hutchinson Cancer Research Center

1:15pm – 1:30pm *Quality improvement assessment of a standardized multidisciplinary approach to prescribing PARP inhibitors*
Amy Indorf, PharmD, University of Washington/Seattle Cancer Care Alliance

1:30pm – 1:45pm *Improving findability of gynecological biospecimens and associated data through the Cascadia Data Discovery Initiative*
Brenda Kostelecky, PhD, Cascadia Data Alliance at Fred Hutch

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SESSION IV: THERAPEUTICS

Moderator **Andre Lieber, MD/PhD** (2010 Pilot Study Award; 2016 Lester and Bernice Smith Challenge Grant)

2:40pm – 2:55pm *Prophylactic in vivo hematopoietic stem cell gene therapy with an immune checkpoint inhibitor reverses tumor growth in syngeneic mouse tumor models*
Andre Lieber, MD/PhD, University of Washington

2:55pm – 3:10pm *Engineering adoptive T cell therapy to co-opt Fas ligand-mediated death signaling in solid tumors*
Kristin Anderson, PhD, Fred Hutchinson Cancer Research Center

3:10pm – 3:25pm *The immune and tumor metabolic ecosystem in human ovarian cancer*
Julian Lum, PhD, BC Cancer Research Centre

3:25pm – 3:40pm *Inflammatory response in endometrial carcinoma is associated with tumor phenotype and host exposures in the Nurses' Health Study*
T. Rinda Soong, MD/PhD, University of Washington

3:40pm – 3:45pm **Closing Remarks by Nora Disis, MD**

SESSION V: POSTER SESSION

3:45pm – 5:00pm **Poster Presentations**

5:00pm – 6:30pm **RECEPTION**

POSTERS

A CLIA certified functional precision medicine assay, the PARIS© test, to predict drug response for ovarian cancer
Carla Grandori, MD/PhD, SEngine Precision Medicine

Single-cell sequencing to investigate the cellular origins of endometrium-derived ovarian carcinomas
Germain C. Ho, BC Cancer Research Centre

CDK4/6 and MEK inhibitor combination in low-grade serous ovarian cancer cell lines
Joshua Hoenisch, University of British Columbia

Potential for vitamin D in the prevention of ovarian cancer in women with BRCA1 mutations
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Single cell proteomic analysis of the tumoral heterogeneity in response to PARP inhibitor
Marilyne Labrie, PhD, Oregon Health and Science University

Targeting FANCD2 increases chemosensitivity of ovarian cancer cells
Tanja Pejovic, MD/PhD, Knight Cancer Institute / Oregon Health and Science University

Selective killing of SMARCA4-deficient ovarian cancer by mitochondria respiration inhibitors
Yemin Wang, PhD, BC Cancer Research Centre

Microbiome profiling of fallopian tubes
Bo Yu, MD, University of Washington

PLANNING COMMITTEE

Mark Carey, MD, University of British Columbia
Kiran Dhillon, PhD, Rivkin Center for Ovarian Cancer
Nora Disis, MD, University of Washington / Fred Hutch
Jackie Lang, PhD, Rivkin Center for Ovarian Cancer
Gordon Mills, MD/PhD, Oregon Health and Science University

Piloting a meditation intervention for ovarian cancer survivors to change Heart Rate Variability (HRV)

Robyn Andersen | Faculty at Fred Hutchinson Cancer Research Center **[Rivkin Pilot Study Awardee]**

Novel Therapies, Survivorship Quality of Life

Most women with ovarian cancer (OC) experience distress. Cancer-related chronic distress appears to promote cancer growth, metastasis, and shorten survival. While it is unclear what all mechanisms connect distress and cancer progression, recent research emphasizes the role of dysregulated activation of the sympathetic nervous systems. This report describes a pilot study of a meditation-based intervention, called Building Personal Resilience (BPR) (15) on levels of perceived stress and HRV in ovarian cancer survivors. The BPR intervention is a supportive intervention designed to reduce distress, and increase the experience of positive emotions through the practice of mindfulness-like breath control exercises. We enrolled eleven ovarian cancer patients who had completed primary therapy in a pilot study to evaluate the feasibility of a smart-phone application assisted version of the BPR meditation-based intervention including heart rate variability feedback that would reduce levels of distress and increase heart rate variability (HRV). Measures of distress included assessments of cancer worry, perceived stress, anxiety, and positive moods. Changes to HRV were also assessed. HRV is a measure of overall nervous system regulation, associated with progression and survival in cancer patients including those with ovarian cancer. We found that cancer survivors were able to fully participate in the intervention and reported the exercises to be helpful. Ten of the 11 reported participating in the exercises with the feedback monitor at least daily, and several reported also using the exercises when they experienced personal challenges independent of their practice schedule. At enrollment, HRV levels in ovarian cancer survivors were low and after intervention had improved ($p < 0.05$). After intervention women reported less cancer worry and greater feelings of calm ($p < 0.05$). Conclusion: An HRV feedback-based mediation intervention for women who have completed ovarian cancer treatment is feasible, acceptable, and reduces cancer worry, while increasing feelings of calm. We also found improvements in HRV associated with the study intervention. Further study of this intervention may provide insights into the influence of autonomic nervous system function on molecular mechanisms of cancer.

[Oral Presentation] **Poster #12**

Engineering adoptive T cell therapy to co-opt Fas ligand-mediated death signaling in solid tumors

Kristin Anderson | Postdoctoral Fellow at Fred Hutchinson Cancer Research Center

Animal Models, Immunology, Tumor Microenvironment

Shannon K. Oda, Breanna M. Bates, Madison G. Burnett, Edison Y. Chiu, Magdalia L. Suarez Gutierrez, Nicolas Garcia, Andrew W. Daman

Background: Over 20,000 women are diagnosed with ovarian cancer annually, and over half will die within 5 years. This rate has changed little in the last 20 years, highlighting the need for therapy innovation. One especially promising new strategy employs immune T cells engineered to target proteins uniquely overexpressed in tumors, with the potential to limit tumor growth without toxicity to healthy tissues. Mesothelin (Msln) is a rational target for ovarian cancer immunotherapy - it contributes to the malignant and invasive phenotype in these tumors and has limited expression in healthy cells.

Methods: Deep transcriptome profiling of whole tumor tissue was used to confirm the expression of similar gene signatures in human cancers and in the preclinical ID8-VEGF mouse model, including comparable expression of immunosuppressive pathways. For example, RNA sequencing, flow cytometry and immunohistochemistry analysis revealed consistently high expression of the immunomodulatory protein Fas ligand (FasL). Human/mouse T cells were engineered to express a human/mouse Msln-specific high-affinity T cell receptor (TCRMsln) and tested for cytotoxic activity against human patient-derived or ID8-VEGF mouse ovarian cancer cell lines in vitro and in vivo.

Results: In a disseminated ID8-VEGF tumor model, adoptively transferred TCRMsln T cells preferentially accumulated within established tumors, delayed ovarian tumor growth, and significantly prolonged mouse survival. However, our data also revealed that elements in the tumor microenvironment (TME) limit engineered T cell persistence and anti-cancer activity.

We and others previously detected FasL in the tumor vasculature and TME of human and murine ovarian cancers. FasL can induce apoptosis in infiltrating lymphocytes expressing Fas receptor (Fas). To overcome this potential T cell evasion mechanism, we generated a panel of immunomodulatory fusion proteins (IFP) containing the Fas extracellular binding domain fused to a CD28 or 4-1BB co-stimulatory domain, rather than the natural death domain. Relative to T cells modified with only TCRMsln, T cells engineered to express both TCRMsln and a Fas IFP preferentially infiltrate tumors, expand/persist and retain function in the TME of tumor-bearing mice. Moreover, adoptive immunotherapy with IFP+ T cells significantly prolonged survival in tumor-bearing mice, relative to TCRMsln T cells lacking an IFP.

Conclusions: Fas/FasL signaling can mediate T cell death, including activation-induced cell death, an apoptotic mechanism responsible for regulating T cell expansion. Thus, tumor cells may upregulate FasL for protection from tumor-infiltrating lymphocytes. As many solid tumors overexpress FasL, IFPs may provide an opportunity to enhance engineered adoptive T cell therapy against many malignancies.

[Oral Presentation] **Poster #20**

Single cell RNA sequencing of normal endometrial organoids reveals prognostic markers in gynecologic tumors

Dawn R. Cochrane | Staff Scientist at BC Cancer

Biomarkers, Etiology/Pathophysiology

Kieran R. Campbell[1], Kendall Greening[2], Germain C. Ho[1], James Hopkins[1], Minh Bui[1], Vassilena Sharlandjieva[1], Daniel Lai[1], Maya DeGrood[2], Evan W. Gibbard[2], Samuel Leung[2], Angela S. Cheng[3], Christine Chow[3], Jamie L.P. Lim[4], Samantha Neilson[1], David Farnell[3], Friedrich Kommoss[5], Jessica N. McAlpine[3], Sohrab P. Shah[4], David G. Huntsman[1]

1. BC Cancer; 2. University of British Columbia; 3. Vancouver General Hospital; 4. Memorial Sloan Kettering Cancer Center; 5. Tubingen University Hospital

Endometrial epithelium gives rise to both endometrial and ovarian cancers (of clear cell and endometrioid subtypes), the latter arising via endometriosis (ectopic endometrium). The endometrium contains two types of epithelial cells, the majority being secretory cells and a minor population of ciliated cells. Since the ciliated cells are rare, little is known about their biology and function in the endometrium. To gain further understanding of the biology of endometrial epithelium, and by extension the cancers that arise from it, we cultured organoids derived from normal endometrial tissue. Notch signaling inhibition induces ciliated cell differentiation and we used this as a strategy to enrich the organoid cultures for ciliated cells. We used single cell RNA sequencing of the organoid cultures to discover new markers for secretory and ciliated cells. We then tested whether these cell type specific markers were expressed in endometrial tumors. Both MST, a secretory cell marker, and FAM92B, a ciliated cell marker, exhibited diffuse staining and were markers of better prognosis. This suggests that tumors expressing differentiation markers have better prognosis, whether it is a marker of secretory or ciliated cells. Interestingly, a small number of endometrial tumors stained positive for DYDC2, a ciliated cell marker, however these tumors exhibited a variable staining pattern with 25-50% tumor cells staining intensely, and the remaining tumor cells not staining at all. A similar variable staining pattern had been observed previously with CTH, another ciliated cell marker. Endometrial and ovarian tumor tissue microarrays were stained with DYDC2, CTH and two well established ciliated cell markers, FOXJ1 and p73. For all these markers, a subset of tumors displayed a variable staining pattern and for endometrial cancers, the variable staining was a good prognostic indicator. Single cell sequencing of endometrial tumors has been able to capture these two populations of tumor cells. In ovarian tumors, only variable CTH staining was a significant prognostic indicator. It has been recently demonstrated that Mullerian secretory cells can both self re-new, as well as giving rise to ciliated cells. This suggests that in cancers that arise from the endometrium, some cells retain this ability to give rise to two epithelial populations, both secretory and ciliated cells, and that these tumors are clinically less aggressive. Using single cell sequencing technology on normal tissues to guide development of prognostic markers and provide insight into the biology of the tumors arising from these tissues may be useful for many other tumor types.

[Oral Presentation] **Poster #10**

WEE1 inhibition suppresses tumor growth in cervical cancer cell lines

Ahmed Diab[1] | Fred Hutch

Molecular Mechanisms, Novel Therapeutics

Kaela Allen[2], Denise Galloway[1] & Bruce Clurman[1]

1. Fred Hutch, Seattle WA; 2. University of Chicago, Chicago, IL

We previously identified a particular sensitivity of HPV-associated head and neck cancers to WEE1 inhibition by small molecule inhibitor AZD1775 both *in vitro* and *in vivo*. Our findings were also corroborated clinically where we observed remarkable response among HPV+ head and neck cancer patients who were treated with neoadjuvant AZD1775 in combination with standard of care chemotherapy.

Here we extended our investigation to cervical cancer cell lines since cervical cancer remains the most common HPV-associated malignancy. Standard of care therapy with chemoradiation does not result in durable cure hence the need for better therapeutic options.

We tested the effect of WEE1 inhibition on the growth of HPV+ cervical cancer cell lines: SiHa, HeLa and Ca Ski in drug washout experiments. We also tested the effect of WEE1 inhibition on cervical retinoblastoma cell line C-33 A.

Inhibition of WEE1 suppressed the growth of HPV+ cervical cancer cells. Moreover, expression of HPV oncoproteins E6 and E7 in human foreskin keratinocytes sensitized them to WEE1 inhibition. Interestingly, HPV-negative C-33 A cells were also sensitive to the WEE1 inhibitor.

Our findings suggest WEE1 as a potential target for cervical cancer treatment confirm that HPV-associated sensitivity to WEE1 inhibition may extend beyond HPV-associated oropharyngeal cancers.

[Poster Presentation] **Poster #23**

Ethnic disparity in detection of ovarian malignancy

Charles Dunton | GYN Oncologist, Medical Director at ASPiRA Labs, a Vermillion company

Biomarkers, Clinical Research

Rowan G Bullock, Herbert Fritsche

Background: Based on evidence that African-American (AA) women have lower CA125 values than Caucasian (C) women, all other factors being equal, we investigated this disparity to see if this would have an impact on ovarian cancer detection using CA125, Risk of Malignancy Algorithm (ROMA), and multivariate index assay (MIA).

Methods: Serum samples from two prospective trials of 1029 women, for which 274 women diagnosed with malignancy were analyzed for CA125 values, ROMA scores, and MIA results. Biomarker data was obtained from the previous prospective studies which validated the MIA test. Of these, 250 women were Caucasian (C) and 24 African-American (AA). Sensitivity, specificity, positive and negative predictive values and confidence intervals for preoperative test results were calculated. CA125 was analyzed at a cutoff point of 200 U/ml and 67 U/ml for premenopausal women.

Results: Sensitivity of MIA in Caucasian women was 93.2% (90.0-96.3%). In African American women, MIA sensitivity was 79.2% (62.9-95.4%). Sensitivity in Caucasian women was 74.4% (68.5-79.7%) for CA125 at the 200 U/ml cutoff, and 80.4% (74.9-85.1%) at the 67 U/ml cutoff. In African American women, sensitivity was 33.3% (15.6-55.3%) for CA125 at the 200 U/ml cutoff, and 62.5% (40.6-81.2%) at the 67 U/ml cutoff. ROMA sensitivity was 82.9% (78.0-87.7%) in Caucasian women and 54.5% (33.7-75.3%) in African American women.

Conclusion: Our results support that CA125 and ROMA in women with adnexal masses have lower sensitivity than MIA. Implementation of MIA in evaluation of adnexal masses should increase sensitivity of detection of malignancy compared to CA125 or ROMA, with the most marked difference being in African American women.

[Oral Presentation] **Poster #7**

Clinical tissue proteomics identifies new mesonephric carcinoma biomarkers

Evan Gibbard | Graduate Student at University of British Columbia

Biomarkers, Diagnostics

Dawn Cochrane[1], Jennifer Pors[2], Basile Tessier-Cloutier[2], David N. Farnell[2], Shane Colborne[3], Angela Cheng[4], Gregg Morin[3], Dietmar Schmidt[5], Stefan Komoss[6], Friedrich Kommoss[7], Blake Gilks[2,4], Jessica McAlpine[8], David Huntsman[1,2,4,5], Lien Hoang[2,4]

1. Molecular Oncology, BC Cancer Agency, Vancouver, BC, Canada; 2. Department of Pathology and Laboratory Medicine, Vancouver General Hospital and The University of British Columbia, Vancouver, BC, Canada; 3. Michael Smith Genome Sciences Centre, BC Cancer Agency, Vancouver, BC, Canada; 4. Genetic Pathology Evaluation Center, Vancouver, BC, Canada; 5. Institute of Pathology and Cytology, Viersen, Germany' 6. Tubingen University Hospital, Tubingen, Germany; 7. Institute of Pathology, Campus Bodensee, Friedrichshafen, Germany; 8. Department of Gynecology and Obstetrics, The University of British Columbia, Vancouver, BC, Canada

Mesonephric carcinoma (MC) and female adnexal tumors of probable Wolffian origin (FATWOs) are challenging to diagnose due to their rarity and morphologic similarities to other gynecologic tumors. There is therefore an unmet clinical need for improved diagnostic techniques to identify these tumors. MCs and FATWOs are thought to arise from developmental remnants of the mesonephric duct. Given their unique tissue of origin, MCs and FATWOs may be distinguishable from other gynecologic malignancies on the basis of shared molecular features. The identification of protein biomarkers of MCs and FATWOs may improve our knowledge of the biology of these cancers and aid in their diagnosis. We used whole proteome screening to identify candidate protein biomarkers of MC and FATWOs. 9 endometrial mesonephric tumors were compared to 54 endometrial tumors of various subtypes. Candidate protein markers were stained for in FATWOs, MCs, other endometrial tumors, and normal tissues by immunohistochemistry. Preliminary analysis indicates that EHMT2, EEF1A2, and GSTM3 have higher levels of expression in MC and FATWOs than endometrial tumors. Protein biomarkers identified in this study may be used to help support the diagnosis of these rare and morphologically cryptic tumors.

[Oral Presentation] **Poster #6**

A CLIA certified functional precision medicine assay, the PARIS© test, to predict drug response for ovarian cancer

Carla Grandori | CEO/CSO at SEngine Precision Medicine

Functional Precision Medicine-Diagnostics

Annie Richardson[*1], Alexandra Dullea[*1], Rachele Rosati[1], Adam Whitney[1], Hallie Swan[1], Michael Churchill[1], Stephanie Tatem Murphy[1], Kathleen Hanson[1], Hartmut Stecher[3], Shalini Pereira[1], Fernanda Musa[2], Franz X Schaub[1], Astrid Margossian[1], Carla Grandori[1]

*Contributed equally. 1. SEngine Precision Medicine, 401 Terry Ave N, Seattle, WA; 2. Swedish Cancer Institute, 1101 Madison Street, Seattle, WA; 3. Cancer Treatment Navigator®, P.O. Box 22887, Seattle, WA

Introduction: Ovarian cancer is one of the leading causes of cancer death among women, with five-year survival rates at around 30%. Most patients present with advanced tumors and are treated with surgical intervention and aggressive combination chemotherapy, and a quarter of patients relapse with chemotherapy resistance. Additionally, there are few actionable genetic targets recurrently seen in ovarian cancers. With this state of the field, functional precision medicine such as the PARIS© test based on 3D culture of tumor-derived organoids can highlight sensitive and personalized drug options to women who have exhausted other treatment options. The PARIS© assay, developed by SEngine Precision Medicine, is a CLIA-certified (Clinical Laboratory Improvement Amendment) high-throughput and high-complexity laboratory-developed test. It enables to measure drug sensitivity across a comprehensive collection of oncology drugs and it is applicable to all solid tumors. To date, the test has been employed for 296 cancer specimens comprising >20 tumor types.

Methods: Here we describe 12 cases of ovarian cancer for which organoids were derived from either ascites, core biopsies or surgical excisions, and subsequently subjected to the PARIS© test. Targeted sequencing of the specimen (available for 10/12 cases) will be presented. Patients were consented under SEngine Precision Medicine IRB research protocol.

[Poster Presentation] **Poster #15**

The effect of OCP use on the incidence of pre-cancerous p53 lesions in fallopian tube fimbria

Kendall Greening | Graduate Student at BC Cancer Research Centre

Prevention

Dawn Cochrane, Dave Farnell, Anthony Karneziz, Gillian Hanley

Background: High grade serous ovarian cancer (HGSOC) accounts for >70% of ovarian cancer related deaths and is the most common ovarian cancer histotype, most originating from pre-cancerous p53 lesions in the fallopian tube (FT) fimbria. Use of oral contraceptive pills (OCPs) for 5 years or more is associated with >40% reduction in risk of HGSOC, but the mechanism is unknown. We hypothesize that OCP use reduces the incidence of p53 lesions. Our preliminary data show higher incidence of p53 lesions in post- compared to pre-menopausal women, therefore we aim quantify p53 lesions in post-menopausal women who previously did or did not use OCPs. This will provide insight into the protective effects of OCPs against HGSOC.

Preliminary results: We determined the presence of p53 lesions by immunohistochemistry (IHC) in FT of women up to 40 years old (n=27) and >60 years old (n=24) who underwent salpingectomies for non-cancer reasons. p53 lesions were identified in 3/27 cases of the younger cohort (11%) and in 10/24 of the older cohort (42%). Thus, we conclude an increased incidence of p53 lesions in older compared to younger women.

Proposed Design: IHC for p53 will be performed on FT fimbria of women >50 years old who received salpingectomy/hysterectomy for non-cancer reasons. Based on an assumed reduction in p53 lesions of 35% in women who used OCPs for 5 years or more compared to non-users (25 vs. 42%), analysis of 190 cases from each group will provide >80% power ($p<0.05$). Cases will be identified through Population Data BC and blind analysis by p53 IHC will be performed at the Vancouver General Hospital. Post-menopausal status will be confirmed by endometrium histology and data flowed back to Pop Data BC to compare to OCP data.

Conclusion: Our preliminary study found that 42% of post-menopausal women had p53 lesions, informing this study design. The study registered through this abstract will be the first to examine the impact of OCPs on the earliest known precursors of HGSOC.

[Oral Presentation] **Poster #4**

Single-cell sequencing to investigate the cellular origins of endometrium-derived ovarian carcinomas

Germain C. Ho | Research Technician at BC Cancer Research Centre

Biomarkers, Cancer Stem Cells, Etiology/Pathophysiology, Molecular Mechanisms

Dawn R. Cochrane[1], Kieran R. Campbell[1], Kendall Greening[2], James Hopkins[1], Minh Bui[1], Vassilena Sharlandjieva[1], Daniel Lai[1], Maya DeGrood[2], Evan W. Gibbard[2], Samuel Leung[2], Angela S. Cheng[3], Christine Chow[3], Jamie L.P. Lim[4], Samantha Neilson[1], David Farnell[3], Friedrich Kommoss[5], Jessica N. McAlpine[3], Sohrab P. Shah[4], David G. Huntsman[1]

1. BC Cancer, Vancouver, BC; 2. Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC; 3. Vancouver General Hospital, Vancouver, BC; 4. Memorial Sloan Kettering Cancer Centre, New York City, NY; 5. Tubingen University Hospital, Tubingen, Germany

INTRODUCTION: Ovarian cancer persists as the 5th deadliest cancer in women, and the 1st among those impacting the gynecological tract. Epithelial ovarian cancers are sub-divided by histotype, the majority of which are characterized as serous, endometrioid (ENOC), clear cell (CCOC), and mucinous ovarian carcinomas. Recent work has shown that both ENOC and CCOC arise from endometrial tissue through processes such as endometriosis; however, a significant knowledge gap remains – "What enables the tissue to develop into 2 distinctly different histotypes?". In a previous study, we proposed that cell of origin may play an instrumental role in tumorigenesis of these different histotypes. Specifically, CCOC and ENOC propagate from cells primed for ciliated cell and secretory cell differentiation respectively. Physiologically, Notch pathway inhibition drives cells towards the ciliated-lineage; we exploit this pathway to enrich and study the normally nominal ciliated cell population in a human organoid system and characterize the cells through single-cell RNA sequencing (scRNA-seq) and single-cell ATAC sequencing.

METHODS: Healthy endometrial tissue was obtained from consented patients receiving surgery for non-cancer-related reasons at UBC and Vancouver General Hospitals. Tissue was digested, cultured shortly as a monolayer and then moved to an organoid system in Matrigel. Organoids were grown out for 5-7 days and treated with the notch pathway inhibitor DBZ for up to 14 days.

RESULTS: As hypothesized, the notch pathway inhibitor DBZ was able to drive ciliated cell differentiation in human endometrial organoids. Through scRNA-seq we were able to identify many distinguishing markers of ciliated cells, but in line with literature, very few secretory-specific markers. Many transcripts expressed in secretory cells were similarly expressed in ciliated cells, informing that ciliated cells are secretory-like cells with the addition of cilia. Markers of ciliated cells (FAM92B, WDR16, and DYDC2) and secretory cells (MST) were validated by immunohistochemistry on normal gynecological tissue sections (fallopian tube and endometrium). Co-immunofluorescence with acetyl-tubulin, a known marker of ciliated cells, were also done on organoid sections. In a separate study, we compare these markers to clinical cancer data and tumour staining, including scRNA-seq done on tumors.

CONCLUSIONS: This study highlights organoid models as a novel method for studying specific cell populations and identifying cellular markers in a more physiologically relevant system than traditional 2D cell culture. These techniques can be adapted to study other cancers and provide impactful insight into cellular origin of tumours.

[Poster Presentation] **Poster #1**

CDK4/6 and MEK inhibitor combination in low-grade serous ovarian cancer cell lines

Joshua Hoenisch | Graduate Student at the University of British Columbia

Novel Therapies

Hannah Kim, Amy Dawson, Nicole Lam, Madison Binder, Gillian Okura, David G Huntsman, Gabriel Dimattia, Greg Morin, Martin Kobel, Blake Gilks, Dane A Cheasley, Kylie Gorringe, Ian Campbell, Raunak Shresta, Collin Collins, Marta Llaurado Fernandez, Mark S Carey

Background: Low-grade serous ovarian cancer (LGSC) is a rare tumor type that requires effective therapies. CDKN2A/B (p16/p15) loss and oncogenic mutations in MAPK genes are common genetic aberrations found in these tumors. We aimed to evaluate CDK4/6 inhibitor (palbociclib) activity, with and without MEK inhibitor (trametinib) treatment, in LGSC cell lines.

Methods: Nine LGSC cell lines (from advanced/recurrent cases) were used to evaluate the effects of palbociclib treatment, with and without trametinib, on cell proliferation (Incucyte) and viability (MTS). Cell cycle gene and protein expression status (p16, CDK4, CDK6, Rb, p-Rb, CCDN1 and E2F) were characterized using whole-exome sequencing and western blot analysis. CDKN2A and RB1 gene copy-number (CN) data and P16 immunohistochemistry staining were obtained from 70 LGSC FFPE tumors and correlated with patient overall survival (OS).

Results: Palbociclib treatment had cytotoxic effects on one LGSC cell line (11%). Presence of CDK4/CDK6 protein expression was observed in 100% of the lines. Absence of p16 and Rb1 expression was detected in 78% (7/9) and 44% (4/9) of lines, respectively, and did not correlate with gene copy number status. Interestingly, none of the lines had detectable mutations in the cell cycle genes screened. Trametinib-resistant lines expressed total and phosphorylated Rb1 but palbociclib treatment did not result in drug synergistic effects. CDKN2A and RB1 copy number loss was detected in 21% and 7% LGSC tumors (all stages), respectively. The prognostic value of CDKN2A/RB1 expression in LGSC tumors is under evaluation.

Conclusions: Palbociclib (with and without trametinib) showed poor activity in LGSC in-vitro, and its activity did not correlate with either p16 or Rb1 expression. Our data suggest that other factors in addition to Rb-proficiency determine palbociclib efficacy in LGSC. Therefore, future translational research to define predictive biomarkers of palbociclib efficacy is needed.

[Poster Presentation] **Poster #17**

Quality improvement assessment of a standardized multidisciplinary approach to prescribing PARP inhibitors

Amy Indorf | Clinical Oncology Pharmacist at University of Washington /Seattle Cancer Care Alliance

Clinical Research, Quality Improvement

Laura Alwan, Abby Miske, Erica Diamantides, Elizabeth Swisher

In 2018, the Hematology/Oncology Pharmacist Association (HOPA) released recommendations for Management of Oral Oncolytic Therapy. The key areas for pharmacist involvement were related to ensuring safe prescribing patterns, conducting comprehensive medication reviews, providing patient education, ensuring proper drug distribution and patient access, and monitoring adverse effects and adherence. The Gynecologic Oncology clinic at the University of Washington Medical Center (UWMC) and Seattle Cancer Care Alliance (SCCA) increased the use of poly (ADP-ribose) polymerase inhibitors (PARPi) as FDA approvals expanded in ovarian cancer. We evaluated practices around the management of these complex medications. Previously, PARPi therapy was initiated and managed without involvement from the oncology pharmacists on the team; the process was cumbersome to nurses and providers, was not standardized, and involved paper records. This led to inefficiencies in tracking and monitoring doses and dose changes, and gaps or inaccuracies in documentation in the electronic medical record (EMR). There were challenges and delays in getting insurance authorization and patients did not fill PARPi prescriptions with the health-system's pharmacy, resulting in uncaptured revenue. To improve this process, we implemented a multidisciplinary, standardized approach to PARPi management.

The multidisciplinary team, including pharmacists, pharmacy technicians, advanced practice providers, clinical nurses, and physicians, created a PARPi workflow and clinical management algorithm. The workflow addressed insurance authorization, drug procurement, and patient education by the pharmacist. The algorithm addressed provider follow-up, monitoring and recommended dose modifications. These were implemented as a pilot in February 2019. Historical data were collected to evaluate time to insurance authorization, insurance denial reasons, and accurate documentation of PARPi in the EMR before the pilot. After pilot implementation, data were collected for the points above, as well as average co-pay amount for patients that used the health-system's pharmacy.

Prior to the pilot, the prescription capture rate for PARPi by the health system's pharmacy was 0%. The rate of accurate documentation of PARPi therapy in the EMR was 34%. At the time of abstract submission, 21 patients were enrolled in the pilot. Fifteen patients have started therapy with a median co-pay of $0 for a 1-month supply (range $0-$2577) with 90% paying less than $100 per month. Prescription capture rate for our pharmacy was 64% and average time to authorization was 2 days.

Ongoing data collection will include patient adherence assessments, pharmacist interventions, adherence to the PARPi management algorithm and dose modifications pre- and post-implementation of the algorithm. Lastly, PARPi selection based on patient factors and comparison of safety and efficacy between agents will be evaluated to update the PARPi management algorithm.

[Oral Presentation] **Poster #14**

Potential for vitamin D in the prevention of ovarian cancer in women with BRCA1 mutations

Sonali Joshi | Research Associate at Oregon Health Science University

Novel Therapies, Prevention

S. Campbell, A. Vrvilo, F. Xu, J. Xu, T. Pejovic

Epithelial ovarian cancer is a lethal gynecological malignancy. Women with inherited mutations in the breast cancer type I susceptibility gene (BRCA1+) have a higher probability of developing ovarian cancer. There is a need to develop effective prevention strategies for BRCA1+ women. Vitamin D (VD) is a steroid hormone that binds to the vitamin D receptor (VDR) and regulates expression of genes critical for cell proliferation, differentiation and apoptosis. Serum VD levels were measured in blood samples from control (n =19) and BRCA1+ cancer-free (n = 12) women. BRCA1+ cancer-free women had lower serum VD levels compared to controls. We sought to determine the efficiency of VD signaling in ovarian surface epithelial (OSE) cells from BRCA1+ cancer-free women and the cellular response to VD treatment in vitro. Immunohistochemistry was performed on ovarian sections from control (n = 5) and BRCA1+ cancer-free (n = 4) women to determine VDR expression in OSE. VDR expression was evident in OSE of ovaries from control women and was attenuated in BRCA1+ cancer-free women. VDR expression in cultured OSE cells was elevated in response to VD treatment in both control and BRCA1+ cancer-free women. We also observed that high doses of VD treatment were associated with low OSE cell proliferation rates in vitro for both groups. Thus, we showed that the efficiency of VD signaling was limited in BRCA1+ women, which could be enhanced by VD-induced VDR expression. Future studies will investigate the relationship between impaired VD signaling and ovarian cancer incidence in BRCA1 carriers.

[Poster Presentation] **Poster #5**

Improving findability of gynecological biospecimens and associated data through the Cascadia Data Discovery Initiative

Brenda Kostelecky | Director, Cascadia Data Alliance at Fred Hutch

Chemoresistance, Clinical Research, Etiology/Pathophysiology, Molecular Mechanisms, Tumor Microenvironment

Aline Talhouk, Elizabeth Swisher, Tanja Pejovic, Ryan Woods, Joe Nooraga, Carly Strasser

Difficulties in finding and accessing biospecimens and data are substantial barriers to translational research. Many gynecologic oncology researchers need access to specimens and associated data to answer questions about etiology, detection, diagnosis, progression, treatment, and outcomes. Broader specimen and data access would enable research on pressing spatial and temporal questions related to cancer metastasis, progression, and development of resistance. Unfortunately, sample collection is expensive and time-consuming and there are often insufficient numbers of relevant samples at any single institution to power studies. Specimen and data sharing could help address such challenges, though simply finding relevant specimens and data available for sharing is challenging. The Cascadia Data Discovery Initiative (CDDI) aims to improve findability of research data in the Pacific Northwest region, including biospecimen information and associated data. Current CDDI collaborating institutions include Fred Hutch, BC Cancer, OHSU Knight Cancer Institute, University of British Columbia, and University of Washington, with support provided by Microsoft.

We have established a CDDI demonstration project that aims to improve findability of gynecologic cancer biospecimens and associated data by sharing metadata (i.e. descriptive information about samples and associated data). This project will inform the development of technology and governance tools and approaches for biospecimen metadata discovery and demonstrate proof-of-concept for scientific utility. Improved discovery will facilitate cohort finding, identification of specimens and datasets for data pooling or complementation, ability to perform preliminary experiments, and training and validation of computational models.

In this project, we are collecting information about researchers' data needs and identifying datasets matching those needs to aid development of metadata discovery tools for the CDDI platform and as a proof-of-concept for the platform's utility. Participating-researcher input is then being used to iteratively improve tool utility. A metadata extraction tool will allow researchers to upload metadata easily and without revealing protected health information. Search and subscribe features will enable identification of relevant datasets and will allow researchers to register interest in certain types of data and receive notification when new data is available. We are also developing governance tools to enable rapid sharing of the underlying data (and/or specimens) after researchers have found data they would like to use through the CDDI metadata-sharing platform. We are actively seeking additional collaborating investigators who would like to find biospecimens or associated data, as well as researchers who have biospecimen repositories or biospecimen-associated data they are interested in sharing (e.g. genomic data, imaging). Interested researchers can contact CDDI at cascadia@fredhutch.org.

[Oral Presentation] **Poster #16**

Single cell proteomic analysis of the tumoral heterogeneity in response to PARP inhibitor

Marilyne Labrie | Postdoctoral Fellow at Oregon Health Sciences University

Proteomics/Metabolomics

Nicholas D Kendsersky[1], Hongli Ma[1], Yong Fang[1], Lydia G. Campbell[1], Jenny Eng[1], Sanghoon Lee[2], Koei Chin[1], Shannon N. Westin[3], Gordon B. Mills[1,2]

1. Knight Cancer Institute and Cell, Developmental and Cancer Biology, Oregon Health and Science University, Portland, OR, USA; 2. Department of Systems Biology, University of Texas, MD Anderson Cancer Center, Houston, TX, USA; 3. Department of Gynecologic Oncology and Reproductive Medicine, University of Texas, MD Anderson Cancer Center, Houston, TX, USA

Although poly (ADP-ribose) polymerase (PARP) inhibitors have shown efficacy in the treatment and maintenance of ovarian cancer patients, development of PARP inhibitor resistance is frequent. Our group and others have demonstrated that the cancer cells adaptive responses to PARP inhibitor can be detected at the protein level and targeting these adaptive responses increase the depth and duration of treatment and might prevent the development of drug resistance. However, it is still unclear if these adaptive responses are conserved across cancer cells from a same tumor and across cells from different lesions. Having a better understanding of the heterogeneity of adaptive responses might help develop better approaches of PARP-based combination therapies. The objective of this study was to develop a single cell proteomic approach to investigate the heterogeneity of adaptive responses in ovarian cancer tumors. We developed a cyclic-immunofluorescence antibody panel and measured the expression of more than 40 proteins at the single cell level in several ovarian cancer tumors that have been treated with PARP inhibitors. We also performed reverse-phased protein array (RPPA) analysis on protein extracted from the tumors and measured the activity of several pathways know to be altered in response to PARP inhibitors. Overall, our results demonstrated that adaptive responses can be detected at the single cell level through cyclic-immunofluorescence. Furthermore, although RPPA assays capture the main pathways alterations in response to PARP inhibitors, cyclic-immunofluorescence adds complementary information by allowing a spatial oriented analysis of the different cell populations as well as their frequency. Overall, this approach might lead to a better understanding of how cancer cells try to survive therapeutic stress and improve the decision making process in the treatment of ovarian cancer patients.

[Poster Presentation] **Poster #11**

Prophylactic in vivo hematopoietic stem cell gene therapy with an immune checkpoint inhibitor reverses tumor growth in syngeneic mouse tumor models

Andre Lieber | Faculty at University of Washington **[Rivkin Challenge Grant Awardee]**

Animal Models, Novel Therapies

Chang Li, Meredith M. Course, Iain Mc Neish, Paul N. Valdmanis

Population-wide testing for cancer-associated germline mutations has established that more than one-fifth of ovarian and breast carcinomas are associated with inherited risk. Salpingo-oophorectomy and/or mastectomy are currently the only effective options offered to women with high-risk mutations. Our goal is to develop a long-lasting approach that provides immuno-prophylaxis for carriers of inherited mutations. Our approach leverages the fact that at early stages, tumors recruit hematopoietic stem/progenitor cells (HSPCs) from bone marrow and differentiate them into tumor-promoting cells. We have developed a technically simple technology to genetically modify HSPCs in vivo. The technology involves HSPC mobilization and intravenous injection of an integrating HDAd5/35++ vector. We performed in vivo HSPC transduction with a GFP-expressing HDAd5/35++ vector, and 17 weeks later implanted syngeneic TC-1 or rat neu-transgenic mouse mammary carcinoma (MMC) cells. In both models >80% of tumor infiltrating leukocytes were GFP-positive. To control expression of therapeutic transgenes, we developed a miRNA regulation system that is activated only when HSPCs are recruited to and differentiated by the tumor. Based on miRNA profiling of tumor-infiltrating leukocytes, our miRNA regulation system should also be applicable in ovarian cancer patients. We then tested our approach in mouse models using the immune checkpoint inhibitor anti-mPD-L1-gamma1 as a transgene. In in vivo HSPC-transduced mice with implanted MMC tumors, after initial tumor growth, tumors regressed and did not recur throughout the observation period (100 days). The regression was T-cell mediated. anti-mPD-L1-gamma1 expression and associated mild auto-immune reactions ceased once tumors disappeared. “Conventional” treatment of MMC tumor-bearing mice with an anti-mPD-L1 monoclonal antibody had no significant anti-tumor effect, indicating that early, self-activating expression of anti-mPD-L1-gamma1 can overcome the immunosuppressive environment in MMC tumors. Furthermore, we employed an ovarian cancer model (ID8) with “high-risk” germline mutations, namely p53 and brca2 mutations. We showed that our approach can prevent intraperitoneal growth of ID8 p53-/-/brca2-/- tumors in syngeneic mice, both in the prophylaxis and therapy settings (when HSC in vivo transduction is performed AFTER tumor establishment). Studies in mouse models with spontaneous tumor onset are ongoing.

Considering the limited prophylactic options that are currently offered to women with germ-line mutations associated with high-risk of cancer onset, and the increasing numbers of these carriers due to population-wide screening, we believe that our in vivo HSPC gene therapy approach is a promising strategy that addresses a major medical problem.

[Oral Presentation] **Poster #18**

The immune and tumor metabolic ecosystem in human ovarian cancer

Julian Lum | Faculty at BC Cancer Research Centre

Immunology, Proteomics/Metabolomics, Tumor Microenvironment

Marisa Kilgour, Sarah MacPherson, Gillian Carleton, Brenna Pauly, Lauren Zacharias, Ralph J. DeBerardinis

The response to cellular immunotherapy (e.g. adoptive T cell therapy and CAR-T cell) for treating hematological malignancies has energized the field to replicate this success in epithelial cancers. The lack of clinical responses in solid tumors is poorly understood though metabolic competition between tumors and tumor infiltrating lymphocytes (TIL) has emerged as a key driver of immune suppression. Using human samples from the same donor, we observed higher 2-NBDG uptake in tumors compared to TIL. However, OXPHOS metabolism was similar between tumor and TIL. We compared these results to LC-mass spectrometry-based metabolite profiling where we cataloged up to 80 unique metabolites from each sample. In this analysis, PCA uncovered distinct metabolite patterns that were different amongst the matched tumor and TIL samples. These patterns were enriched in metabolites found in purine and arginine biosynthesis which we correlated with the degree of TIL infiltration and patterns of immune gene expression. Thus, TIL and tumors do not appear to exhibit the same patterns of metabolite utilization. Despite these differences, ex vivo expansion of CD8+ T cell using a clinically approved protocol for T cell therapy found evidence of oxidative stress and loss of metabolic fitness over time. These data shed new insight into metabolic behavior of cells in human ovarian cancer.

[Oral Presentation] **Poster #21**

Targeting FANCD2 increases chemosensitivity of ovarian cancer cells

Tanja Pejovic | Faculty at Knight Cancer Institute, Oregon Health & Science University

Biomarkers, Clinical Research, DNA Repair & Response, Molecular Mechanisms

Sonali Josh, Adam Krieg, Toma Conrads

Background: The DNA repair protein FANCD2 functions to suppress DNA damage and cell death in response DNA crosslinking agents. It exerts its DNA damage response function in the nucleus and therefore requires nuclear import to be functional. However, our preliminary data suggest that a subset of ovarian cancers displays predominantly cytoplasmic FANCD2 (cFANCD2) localization and this finding positively correlates with survival. Recent work done by another group demonstrated that FANCD2 nuclear import is dependent upon expression of another protein called CCAT/enhancer Binding Protein Delta (C/EBP-delta).

Objective: Our objective is to determine the mechanisms underlying better prognosis in patients with cFANCD2. We hypothesize is that failure of nuclear import of FANCD2 undermines DNA damage response and determines ovarian cancer cell response to chemotherapy. We tested whether CEBP-delta regulates cFAND2-nFANCD2 subcellular trafficking, thereby regulating cellular resistance to ICLs in vitro.

Results: Women whose tumors were cFANCD2 positive had better survival (median = 52 months) than women who did not (median = 38 months). Although the difference in the survival curves appears modest it confers a non-inconsequential increase in median survival (14 months). In collaboration, we generated OVCAR3 cell line with ablated expression of CEBP-delta and validated shRNA knockdown of CEBP-delta transcript using qPCR and also by immunoblot validation. Cells harboring sh-CEBP delta had reduced FANCD2 foci when exposed to MMC. These cells showed increased sensitivity to carboplatin (50 micromol) in vitro.

Conclusion: Preliminary results show that CEBP-delta inhibition is associated with reduced n-FANCD2 and therefore may regulate its nuclear import. Cells with reduced nFANCD2 have increased sensitivity to platinum. These results could lead to (1) identification of women who will have a better response to platinum-based chemotherapy and (2) identification of a new molecular method (inhibition of FANCD2 nuclear import) for improving the efficacy of platinum-based chemotherapy in women who are refractory to initial platinum treatment.

[Poster Presentation] **Poster #3**

Targeted next-generation sequencing identifies mutations in epigenetic regulators in a large cohort of adult-type granulosa cell tumors

Jessica Pilsworth | Graduate Student at University of British Columbia

Genetics/Genomics/Epigenetics

Dawn Cochrane[2], Samantha Neilson[2], Anniina Färkkilä[3,4], Hugo Horlings[2], Satoshi Yanagida[5], Yi Kan Wang[2], Ali Bashashati[2], Winnie Yang[2], Janine Senz[2], Jacqueline Keul[6], Adele Wong[7], Esther Oliva[7], Stefan Kommoss[6], Friedrich Kommoss[8], Sohrab Shah[9], David Huntsman[2,10]

1. Dept of Medical Genetics, UBC, Vancouver, BC, Canada; 2. Dept of Molecular Oncology, BC Cancer Agency, Vancouver, BC, Canada; 3. Children's Hospital and Dept of Obstetrics and Gynecology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; 4. Harvard Medical School, Dept of Radiation Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; 5. Dept of Obstetrics and Gynecology, The Jikei University School of Medicine, Tokyo, Japan; 6. Tübingen University Hospital, Tübingen, Germany; 7. Dept of Pathology, Massachusetts General Hospital, Boston, MA, USA; 8. Institute of Pathology, Campus Bodensee, Friedrichshafen, Germany; 9. Dept of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center; 10. Dept of Pathology and Laboratory Medicine, UBC, Vancouver, BC, Canada

Background: Adult-type granulosa cell tumors (AGCT) are the most common sex cord-stromal tumor and represent 3-5% of all ovarian cancers. Most patients are diagnosed at an early stage and have indolent tumors. However, one-third of patients relapse, typically 4-7 years after initial diagnosis, leading to mortality in 50% of these relapsed patients. Surgery is the first-line treatment for both primary and relapsed tumors, but there are currently no effective treatments for patients with unresectable or advanced stage tumors. Our research team previously discovered the somatic missense mutation (c.402C>G; pC134W) in the transcription factor Forkhead box L2 (FOXL2) in 97% of AGCTs. This discovery has been developed into a diagnostic biomarker, but our ability to understand the biology of the mutation, pathogenesis of the tumor and develop treatments has been hindered by a lack of appropriate model systems. My project aims to profile the genomic landscape of AGCT and develop a relevant model system to study the impact of FOXL2 and secondary mutations on tumor development. We hypothesize that additional mutations besides FOXL2 are responsible for the clinical variability of AGCT and could represent treatment opportunities.

Methods: We performed whole genome sequencing on ten AGCTs and their matched normal blood. From this analysis we designed a custom amplicon panel to perform targeted sequencing on a cohort of over 200 formalin-fixed paraffin-embedded AGCTs that was collected internationally. For our model system, we used density centrifugation to isolate primary granulosa cells from follicular fluid collected from healthy women undergoing oocyte retrieval and used lentiviral delivery to incorporate select mutations identified from our genomic analysis.

Results: We have successfully developed a model system expressing fluorescently-tagged FOXL2 (wildtype or C134W mutant) and human telomerase (previously identified from our genomic analysis) in primary granulosa cells. Additionally, our whole genome and targeted sequencing analysis on a cohort of over 200 AGCT patients from six countries revealed that two epigenetic regulators, KMT2D and KDM5C, were recurrently mutated with various missense and truncating mutations in 83 (41%) and 26 (13%) of 203 patients, respectively. To study KMT2D truncating mutations, we have cloned CRISPR guide RNAs targeting KMT2D into lentiviruses and are testing their knockout efficiency in the AGCT-derived cell line KGN.

Conclusions: Our large genomic study revealed mutations in epigenetic modifiers, suggesting that epigenetic dysregulation may play a role in the development of AGCT. We plan to knockout KMT2D in our primary cell models (wildtype or mutant FOXL2) to study the impacts on cell viability. Through this project, we will gain insight into the interaction between mutant FOXL2 and epigenetic regulators including KMT2D, which is the first step in developing biologically-informed therapeutics.

[Oral Presentation] **Poster #9**

Characterization of TP53 mutations in Pap test DNA of women with and without serous ovarian cancer

Rosana Risques | Faculty at University of Washington **[Rivkin Pilot Study & Bridge Fund Awardee]**

Biomarkers, Diagnostics, Genetics/Genomics/Epigenetics

Jeffrey D. Krimmel-Morrison[1,2], Shenyi Lian[2], Yuezheng Zhang[2], Jeanne Fredrickson[2], Daniela Nachmanson[2], Kathryn Baker[2], Marc R. Radke[3], Enna Hun[3], Barbara Norquist[3], Mary Emond[4], Elizabeth M. Swisher[3]

1. Department of Medicine, University of Washington, Seattle, WA 98195, USA; 2. Department of Pathology, University of Washington, Seattle, WA 98195, USA; 3. Department of Obstetrics and Gynecology, University of Washington, Seattle, WA 98195, USA; 4. Department of Statistics, University of Washington, Seattle, WA 98195, USA

Objective: The development of Pap tests as a molecular diagnostic for serous ovarian cancer is a promising concept, but previous studies reported limited sensitivity. In addition, the presence of cancer-associated somatic mutations in normal tissue is increasingly recognized as a specificity challenge for mutational tests. We aimed to determine the diagnostic performance of Pap tests for ovarian cancer detection using ultra-accurate deep sequencing.

Methods: We used CRISPR-DS, a novel Duplex Sequencing method that employs CRISPR-based target enrichment to increase efficiency and reduce DNA input. We performed ultra-accurate deep sequencing (mean 2000x) of the TP53 gene in 30 Pap tests from 21 women without cancer and 9 women with serous ovarian cancer with known TP53 driver mutations. Mutations were annotated using the Seshat web service and compared to those in the UMD TP53 cancer database.

Results: The tumor-derived mutation was identified in 3 of 9 Pap tests from women with ovarian cancer (33% sensitivity). In addition, 221 low frequency ($\lesssim$0.001) mutations were identified in the coding region of TP53 in Pap tests from women with ovarian cancer (94 mutations) and without ovarian cancer (127 mutations). In both groups these mutations showed evidence of positive selection as indicated by clustering in exons 5 to 8, preferential location in hotspot codons and CpG dinucleotides, common presence in cancer database, impact on protein activity, and predicted pathogenicity. These 'cancer-like' features were significantly more frequent in mutations identified in women with ovarian cancer than in women without cancer.

Conclusions: Pap tests have low sensitivity for ovarian cancer detection and carry abundant low frequency TP53 mutations. These mutations are more frequently pathogenic in women with ovarian cancer and determining whether their presence is associated with an increased gynecologic cancer risk warrants further study.

[Oral Presentation] **Poster #2**

Inflammatory response in endometrial carcinoma is associated with tumor phenotype and host exposures in the Nurses' Health Study

T. Rinda Soong | Faculty at University of Washington

Tumor Microenvironment, Pathology

Michael Downing[1], Joy Shi[3,4], Evan Busch[3,4], Geraldine S. Pinkus[1], Immaculata De Vivo[3,4], George L. Mutter[1]

1. Department of Pathology, Brigham and Women's Hospital, Boston, MA; 2. current affiliation: Department of Pathology, University of Washington Medical Center, Seattle, WA; 3. Channing Division of Network Medicine, Brigham and Women's Hospital; 4. Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA

Background: Inflammation in invasive carcinoma has been proposed to be a risk modifier of tumor initiation and progression. The role of tumor immune response (TIR) in endometrial carcinoma (EC) is far understudied compared to other malignancies. We aimed to characterize the associations of EC inflammatory response with tumor phenotype and host non-genetic exposures.

Methods: Incident ECs arising in the Nurses' Health Study between 1976 and 2012 were included (n=325). Immune cell densities and biomarker expression within tumors were examined using tissue microarrays, including leukocytes, T helper cells, cytotoxic T cells, FOXP3+ regulatory T cells, B cells, macrophages, plasma cells, as well as levels of DNA damage, estrogen and progesterone receptor expression. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) from multivariable logistic regression models were estimated to evaluate the associations of inflammatory profiles with tumor features and EC risk factors. Immune marker expression was reviewed at different cut points in increments (5-100 cells/mm2) to determine appropriate binary categorizations.

Results: Most (99%) of the subjects were Caucasians and the majority (87%) of ECs in this cohort was of endometrioid subtype. Trends correlated with tumor subtypes included poorly differentiated endometrioid ECs with increased T cells (>=350 cells/mm2), and non-endometrioid ECs with increased macrophages (>=150 cells/mm2). Increased tumor DNA double-strand breaks was associated with mildly increased leukocyte recruitment (>=200 cells/mm2)(aOR: 1.1; 95% CI: 1.1, 1.3). History of rheumatoid arthritis conferred 2-fold increased odds of more T helper cells (>=60 cells/mm2) in EC (aOR: 2.5; 95% CI: 1.1, 5.6). Several immune cell subsets (leukocytes, T cells, T helper cells, FOXP3+ T cells and B cells) were also slightly elevated with longer use of combined estrogen and progesterone hormone therapy (aORs: 1.1-2.0; 95% CIs: 1-2.0). In contrast, former use of aspirin decreased by 3-fold the odds of elevated T cells (aOR: 0.3; 95% CI: 0.1, 0.9) compared to never aspirin use. Longer oral contraceptive use was correlated with reduced levels of cytotoxic T cells (<25 cells/mm2) (aOR: 0.8; 95% CI: 0.7, 0.9) and plasma cells (<7 cells/mm2) (aOR: 0.9; 95% CI: 0.8, 0.9). In addition, obesity (body mass index >30 kg/m2) was associated with decreased FOXP3+ T cells in EC (aOR: 0.3; 95% CIs: 0.2, 0.7).

Conclusions: Our data support the hypothesis that TIR in EC is co-determined by tumor phenotype as well as host physiologic, hormonal and drug exposures. The differential association patterns seen with different immune cell subsets highlight tumor and host risk factors that may promote and suppress TIR in EC. The findings underscore an interaction between TIR and local environment, and inform follow-up studies to investigate whether and how inflammatory pathways in the endometrium may be manipulated to reduce risk of tumor development and spread.

[Oral Presentation] **Poster #22**

Selective killing of SMARCA4-deficient ovarian cancer by mitochondria respiration inhibitors

Yemin Wang | Staff Scientists at BC Cancer Research Centre

Novel Therapies

Dionzie Ong, Shary Yuting Chen, Eunice Li, Valerie Tao Lan and David Huntsman

Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) is a rare but highly aggressive ovarian cancer that mainly impacts young women. Recent genomic studies have demonstrated that SMARCA4 genetic inactivation and protein loss is the key driver of the disease. Through analyzing the publicly available AVANA CRISRP/cas9 genome-wide screen database for about 500 cell lines, we identified that SCCOHT cell lines are selectively sensitive to the genetic ablation of multiple components of mitochondria electron transfer chain (ETC). We validated that both SCCOHT and SMARCA4-deficient dedifferentiated ovarian carcinoma cell lines are remarkably more sensitive to metformin and phenformin, two anti-diabetic drugs that also inhibit ETC complex I, and tigecycline, a selective inhibitor of the mitochondria polymerase POLG, than ovarian high-grade serous carcinoma and clear cell carcinoma cell lines. Re-expression of SMARCA4 downregulated the expression of POLG and several genes encoding subunits of complex I, such as NDUFB9, suggesting that SMARCA4 deficiency may increase both the biogenesis and oxidative activity of mitochondria, which is currently being investigated. Furthermore, phenformin inhibited the growth of SCCOHT tumors in mouse subcutaneous xenograft models. Therefore, these data suggest that selective targeting mitochondria respiratory complex function can be an effective strategy for SCCOHT and other SMARCA4-deficiency driven gynecologic cancers.

[Poster Presentation] **Poster #19**

Microbiome profiling of fallopian tubes

Bo Yu | Faculty at University of Washington **[Rivkin Bridge Fund Awardee]**

Etiology/Pathophysiology

Congzhou Liu, David Fredricks, Elizabeth Swisher

Objectives: Several studies indicate that the female upper genital tract including the fallopian tubes may not be sterile. However, there are many limitations with these studies and the findings were inconsistent. In this prospective study, we collected swabs from the fallopian tubes and other surgical sites as controls in sterile fashion to profile the microbiota in the fallopian tubes.

Methods: After obtaining informed consent from patients, we collected swabs from the fallopian tubes, ovarian surfaces, paracolic gutters, laparoscopic ports, and sham swabs (air in the operating room) in sterile fashion. Surgical indications included ovarian cancers of various histological types, prophylactic salpingo-oophrectomies due to germline BRCA or other mutations, benign gynecological disorders such as ovarian cysts or endometriosis. Exclusion criteria included pelvic inflammatory disease, presence of an intrauterine device, use of antibiotics, endometrial biopsy, intrauterine device removal or hysteroscopy in the 30 days prior to the intended enrollment. DNA was extracted from the swabs and V3-V4 region of 16S rRNA gene was amplified and sequenced, and the bacterial concentrations were quantified using qPCR.

Results: A total of 84 patients were enrolled and 392 swabs were collected. The diagnoses included ovarian cancer (n=37), benign ovarian cysts (n=17) and no pathological findings (n=30). The sites of swab collections included fallopian tubes and ovarian surfaces (n=195 swabs), air (n=38), laparoscopic port (n=14), paracolic gutter (n=54), cervix (n=68), anus (n=23). An example of qPCR results from a batch of the samples is shown in Figure 1. The bacterial concentrations of fallopian tube and ovarian surfaces consistently ranged 10~1000 copies of 16S rRNA genes/ul of DNA, at least 10 times higher than the air or port swabs and dilution buffer controls, and at least 10,000 times lower than the cervical or anal swabs. The types of surgery, cancer status, or histological subtypes did not affect the bacterial concentrations of the samples.

Conclusions: The bacterial concentrations of most fallopian tube samples were slightly but consistently above the negative controls, which may indicate the existence of low level of bacteria in the fallopian tubes. The disease pathology does not affect the bacterial concentration in the fallopian tubes. Taxonomic identification of bacteria is ongoing.

[Poster Presentation] **Poster #13**

Modelling initiation events of low-grade serous ovarian cancers with organoid cultures and single cell sequencing

Joyce Zhang | Graduate Student at BC Cancer Research Centre

Biomarkers, Genetics/Genomics/Epigenetics, Molecular Mechanisms, Proteomics/Metabolomics

Dawn Cochrane[1], Kieran Campbell[1], James Hopkins[1], Genny Trigo[1], Germain Ho[1], Winnie Yang[1], Maya DeGrood[1], Sorab Shah[1,2], David Huntsman[1,2]

1. Department of Molecular Oncology, BC Cancer Research Centre; 2. Department of Pathology and Laboratory Medicine, University of British Columbia

Ovarian cancer is the most common gynecologic cancer and the fifth leading cause of cancer death in women. Such poor outcome is due to lack of reliable early detection strategies and suboptimal response to chemotherapies. Low grade serous carcinoma (LGSC) of the ovary is a rare type of epithelial tumour, accounting for 5% of all ovarian cases. LGSC typically present in young women and have a relatively good prognosis, despite being resistant to chemotherapy.

LGSC is presumed to come from ectopic Müllerian epithelium, and increasing histological and gene expression data have suggested the cell of origin to be secretory cells at the Fallopian tube. In terms of mutational background, LGSC harbours a relatively stable genome, with typical gain of function events affecting BRAF, KRAS and NRAS. Interestingly, LGSC NRAS mutations are found with concomitant EIF1AX mutations. The low incidence of the disease has refrained LGSC to be a poorly understood disease, and the resulting lack of available models further limits the study of the tumorigenesis process and mechanisms of chemo-resistance. Here we propose to use the novel model system, the organoid cultures of Fallopian tube epithelium, to study how NRAS (Q61R) and EIF1AX (G8E) mutations co-operate to drive initial tumorigenesis process of LGSC of the ovary, in hoping to develop better early detection strategies as well as more informed therapeutic options.

Objective: to investigate how NRAS(Q61R) and eIF1a (G8E) mutations drive the early stages of LGSC tumorigenesis, with the organoid system and single-cell sequencing.

Method: Mutations are introduced into primary cells of fimbriated end of Fallopian tube tissues from individuals undergoing surgical procedures for non-cancerous reasons. To model LGSC, activating mutations of Nras(Q61R) and eIF1a (G8E), are introduced along with different fluorescent markers. Organoids are cultured from transduced primary cells, and subsequently histological changes of the mutant organoids will be monitored and changes in gene expression will be resolved with single cell RNA-sequencing (scRNA-seq).

Result: Cytology of LGSC-modeling organoids show intense staining of nuclei, with a few cells show multiple nucleoli and mitotic figures. Pilot scRNA-seq experiment has shown upregulation of genes involved in mRNA translation such as ribosomal subunits, translation initiation and elongation factors.

Conclusion: Organoid culture and with single-cell sequencing represent a powerful duo in studying the initiation events in LGSC of the ovary. Our work is crucial for developing early detection and prevention strategies as well as more informed and targeted treatment options. We plan to seek new treatment options targeting the perturbed pathways as informed by scRNA-seq analysis.

[Oral Presentation] **Poster #8**

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PILOT STUDY AWARDS *in ovarian cancer research*
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Request for Applications

Pilot Study Award Overview:
The Rivkin Center for Ovarian Cancer is announcing funds for approximately twelve Pilot Study Program awards to be allocated based on scientific merit. Pilot Study Program awards will support investigator-initiated projects in all areas of ovarian cancer research. In addition, projects designed to analyze data from already funded clinical trials will be considered. The two year awards will provide a total of $75,000 in funding, with the possibility of an additional $25,000 awarded in year two, upon evaluation of year one progress, contingent on availability of funds. *Funds are for direct costs only; institutional overhead and indirect costs will not be included in the award.*

Applicants may budget for salary support, materials, supplies, consumables, travel costs for scientific meetings, and other expenses as justified. Budget and budget justification must be included with the application.

Funding priority will be given to proposals that are:

- *Innovative*
- *Multidisciplinary*
- *Likely leading to submission of grant applications for independently funded investigations*
- *Conveying translational research potential*

Eligibility:
Investigators at the assistant, associate or full professor level (or equivalent) are encouraged to apply.

Requirements upon funding:
Interim scientific and financial reports must be provided within 30 days following the first anniversary of the start date for the project to be considered for an additional $25,000 in funding for the project. Two projects will be selected per award cycle to receive the additional funding contingent on availability of funds. Final scientific and financial reports must be provided within 90 days after the completion of the funding period. In addition to submitting all final reports and annual updates, award recipients are highly encouraged to present at the next forthcoming Rivkin Center Symposium following the completion of funding. Awardees are eligible to compete for travel stipends from the Rivkin Center in order to defray symposium travel expenses. Award recipients are encouraged to use results to publish findings and develop full-scale funding applications to national agencies.

Application Format and Instructions:
Applicants should submit a proposal application to the Rivkin Center via proposalcentral.com, including applicant/PI and institution contact information, scientific proposal, budget information, biosketch, other support, organizational assurances, and scientific and lay abstracts.

Scientific Proposal: The Scientific Proposal should be no more than five pages in length addressing each of the following areas: Specific Aims, Background and Significance, Preliminary Results (if available), and Research Design and Methods (Arial or other acceptable font, 11 point minimum, 8.5" x 11" paper, 0.5" margins). All tables, figures, and images must fit within the five-page limit and be legible. References should be included and are not counted as part of the five-page limit. Additional materials (e.g. published papers, submitted manuscripts, letters of support, summary of facilities and resources, etc.) will not be considered.

Application Submission:
All application materials should be submitted through proposalCENTRAL by the application **due date (December 2, 2019, 5PM Eastern Time)**. Applicants who do not already have an account in proposalCENTRAL must register for an account prior to beginning application. Once completed, the application must be validated to ensure all materials have been submitted. Signature pages must be printed for a wet signature (not an electronic signature) from the named institutional official and then uploaded to proposalCENTRAL.

More Information:
Visit proposalcentral.com or rivkin.org for the latest Guidelines. Questions may be directed to Kiran Dhillon, PhD at kiran.dhillon@swedish.org or (206) 215-2964.

The Rivkin Center for Ovarian Cancer is an independent 501(c)(3) non-profit organization established in Seattle in 1996 by medical oncologist Saul E. Rivkin MD (retired), in loving memory of his wife Marsha, who lost her life to ovarian cancer. The Rivkin Center invests in cutting-edge research to prevent, detect, and cure ovarian cancer, a deadly and under-funded disease. The Rivkin Center has funded over $13 million in research grants worldwide. For more information, please visit www.rivkin.org or call (206)215-2964.

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SCIENTIFIC SCHOLAR AWARDS *in ovarian cancer research*
$120,000 Two-Year Awards
Request for Applications

Scientific Scholar Award Overview:

The Rivkin Center for Ovarian Cancer is announcing funds for approximately five Scientific Scholar awards to be allocated based on scientific merit. Two-year grants at $120,000 each, Scientific Scholar Awards are intended to assist promising laboratory and clinical scientists in pursuing a career as an independent investigator in ovarian cancer research. *Funds are for direct costs only; institutional overhead and indirect costs will not be included in the award.*

Applicants must budget at least half of each year's award for salary support, including fringe benefits. Applicants may budget remaining funds for materials, supplies, consumables, travel costs for scientific meetings, and other expenses as justified. Budget and budget justification must be included with the application.

Eligibility:

Potential candidates will have an MD, PhD, or equivalent degree with career goals focused on ovarian cancer. Clinicians will have completed their residency. Candidates should be at the post-doc/fellow, instructor, research assistant, or assistant professor level with no more than 3-4 years in any of these positions. Established, outstanding scientists without prior focus in ovarian cancer but looking to focus in this disease area are also encouraged to apply.

Requirements upon funding:

Interim scientific and financial progress reports must be provided within 30 days following the first anniversary of the award start date for Year 2 funds to be issued. Funds for Year 2 will be issued upon satisfactory progress during Year 1, as determined by review of interim progress reports. Final scientific and financial reports must be provided within 90 days after the completion of the funding period. In addition to all final reports and annual updates, award recipients will be required to present at the next forthcoming Rivkin Center Symposium following the completion of funding. The Rivkin Center will provide travel in addition to Scientific Scholar Award funding unless travel funds remain as part of the award. Award recipients are encouraged to use results to publish findings and develop full-scale funding applications to national agencies.

Application Format and Instructions:

Applicants should submit a proposal application to the via proposalCENTRAL (proposalcentral.com) including applicant/PI and institution contact information, scientific proposal, cover letter, mentor's statement(s), career development plan, budget information, biosketch, other support, organizational assurances, and scientific and lay abstracts.

Scientific Proposal:

The Scientific Proposal should be no more than five pages in length addressing each of the following areas: Specific Aims, Background and Significance, Preliminary Results (if available), and Research Design and Methods (Arial or other acceptable font, 11 point minimum, 8.5" x 11" paper, 0.5" margins). All tables, figures, and images must fit within the five-page limit and be legible. References should be included and are not counted as part of the five-page limit. Additional materials (e.g. published papers, submitted manuscripts, letters of support, summary of facilities and resources, etc.) will not be considered.

Cover Letter:

A cover letter must accompany the application and should contain the following information:

- Name of candidate, current title, and institution
- Prior training/experience in ovarian cancer
- Short- & long- term research & career goals
- Name(s) of mentor(s)

Mentor's Statement(s):

Please include a letter(s) of support from the selected mentor(s) including information on his/her relevant experience, his/her commitment to the applicant's research plan, and nature of the supervision that will occur during the award period.

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Release Date: September 1, 2019

Career Development Plan:
The career development plan is closely evaluated and strongly weighed in the review process. The plan must be specifically tailored to the applicant's needs and with the ultimate goal of achieving independence as a researcher. Describe how the award will contribute to the applicant's ability to fulfill both short-term and long-term goals.

A systematic plan should be presented for obtaining the necessary research experiences to launch an independent ovarian cancer research career. The plan must detail additional training and/or classes needed to meet goals.

The plan should identify 1-2 mentors and include a justification for one year of mentored research experience. Describe each mentor's areas of expertise and responsibilities as well as the rationale for the applicant's choice of mentors. A convincing case must be presented to demonstrate that the support of the mentor(s) will substantially enhance the applicant's career and/or will allow the pursuit of a novel or promising study with research objectives. A biosketch must also be included for the mentor(s).

Application Submission:
All application materials should be submitted through proposalCENTRAL by **the application due date (December 2, 2019, 5PM Eastern Time)**. Applicants who do not already have an account in proposalCENTRAL must register for an account prior to beginning application. Once completed, the application must be validated to ensure all materials have been submitted. Signature pages must be printed for a wet signature (not an electronic signature) from the named institutional official and then uploaded to proposalCENTRAL.

More Information:
Visit proposalcentral.com or www.rivkin.org for the latest "Scientific Scholar Award Guidelines." Questions may be directed to Kiran Dhillon, PhD at Kiran.Dhillon@swedish.org or (206) 215-2964.

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BRIDGE FUNDING AWARD *in ovarian cancer research*
$30,000 Six-Month Award
Request for Applications
Release Date: September 1, 2019

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Bridge Funding Award Overview:
The Rivkin Center for Ovarian Cancer is announcing funds for up to one Bridge Funding Award based on scientific merit. The purpose of Bridge Funding is to allow researchers to produce data needed to substantiate their proposal resubmission to federal funding agencies for a promising new research project. The Rivkin Center provides interim funding of up to $30,000 to researchers who have submitted an R01, R21, K08, K23, or K99 proposal to the National Institutes of Health (NIH) or an original proposal to the Department of Defense (DoD) pertaining to ovarian cancer and who have not received, but were close to, a fundable score. Investigator-initiated projects in all areas of ovarian cancer research are eligible. Special consideration will be given to research that has clinical applicability. *Funds are for direct costs only; institutional overhead and indirect costs will not be included in the award.*

Applicants may budget for salary support, materials, supplies, consumables, and other expenses as justified. Budget and budget justification must be included with the application.

Eligibility:
Investigators at all levels are encouraged to apply. Unfunded first submission NIH R01, R21, K08, K23, and K99 proposals (no A1 or A2 proposals) as well as original DoD proposals are eligible for consideration. NIH proposals must have scored in the 19th percentile or lower, and DoD proposals must have scored less than 1.9. Proposals must have received their agency score within the past 9 months. Proposals must require at least six months of additional research work prior to resubmission.

Requirements upon funding:
A final scientific report, final financial report, and lay abstract must be provided within 90 days after the completion of the funding period. The outcome of the resubmission must also be reported to the Rivkin Center.

Application Format and Instructions:
Applicants should submit a proposal application to the Rivkin Center via proposalCENTRAL including applicant/PI and institution contact information, scientific proposal summary, budget information, a copy of the original proposal to NIH or DoD, a copy of the reviewers' Summary Statement evaluating the proposal submitted to NIH or DoD together with responses to the Statement's critiques. Additional materials (e.g. published papers, letters of support) will not be considered. The scientific proposal summary should include three components: (A) Abstract describing the rationale, specific aims, and general methodology of the project (not more than 1 page); (B) Explanation of the potential impact of this research on the understanding, prevention, diagnosis, and/or treatment of ovarian cancer (not more than 1 page); (C) Discussion of how the funds from the Rivkin Center will be used to address the score-driving issues raised in the Summary Statement from the reviewers (not more than 1 page). Be sure to include the expected date of resubmission to NIH or of new submission to DoD**.**

Application Submission:
All application materials should be submitted through proposalCENTRAL by **the application due date (October 15, 2019, 5PM Eastern Time)**. Applicants who do not already have an account in proposalCENTRAL must register (Link for site) for an account prior to beginning application. Once completed, the application must be validated to ensure all materials have been submitted. Signature pages must be printed for a wet signature (not an electronic signature) from the named institutional official and then uploaded to proposalCENTRAL.

More Information:
Visit proposalCENTRAL.altum.com
or www.rivkin.org for the full "Bridge Funding Award Guidelines." Questions may be directed to Kiran.Dhillon@swedish.org.

The Rivkin Center for Ovarian Cancer is an independent 501(c)(3) non-profit organization established in Seattle in 1996 as a joint partnership with Swedish Medical Center and Fred Hutchinson Cancer Research Center. Our mission is to improve women's health by helping them prevent, detect early, and survive ovarian and breast cancer. We do this by investing in cutting edge research to prevent and cure ovarian cancer, a deadly and under-funded disease, educating women to prevent and detect ovarian and breast cancer as early as possible, and fostering an ever growing community of survivors, patients, researchers, clinicians, advocates and supporters. We envision a world where women live longer and healthier lives because their cancers are prevented, caught early, or cured. For more information, please visit www.rivkin.org or call (206)215-6200.