# 2019 UCSF Breast Oncology Program Scientific Retreat

Jewish Community Center San Francisco, 3200 California St., San Francisco, 94118

## Poster Session

*The full poster abstract handout was distributed by email to all retreat participants, and is available on line at http://cancer.ucsf.edu/bop2019.*

*Posters selected to give podium presentation are highlighted in bold font.*

***Therapeutics and Clinical Trials***

#1 Identifying breast cancer molecular phenotypes to predict response in a modern treatment landscape: lessons from ~1000 patients across 10 arms of the I-SPY 2 TRIAL

#2 Complete Pathologic Response Is a Strong Predictor of Event Free Survival and Distant Recurrence Free Survival, Regardless of Tumor Subtype or Investigational Agent, in Women with Early Breast Cancer at High Risk for Recurrence in the I-SPY 2 TRIAL

#3 BluePrint basal subtype predicts neoadjuvant therapy response in ~400 HR+HER2- patients across 8 arms in the I-SPY 2 TRIAL

**#4 TGFβ inhibition sensitizes breast cancer brain metastasis tumors to radiation treatment**

#5 Chemically Designing Therapeutic Enzymes That Bind to Breast Cancer

#6 Palbociclib in Combination with Fulvestrant or Tamoxifen as Treatment for Hormone Receptor Positive (HR+) Metastatic Breast Cancer (MBC) with Prior Chemotherapy for Advanced Disease (TBCRC 035) A Phase II Study with Pharmacodynamics Markers

#7 Clinical significance of circulating tumor cells (CTCs) in hormone receptor-positive (HR+) metastatic breast cancer (MBC) patients receiving letrozole or letrozole plus bevacizumab: CALGB 40503 (Alliance)

***Detection and Biomarkers***

**#1 Personalized serial circulating tumor DNA (ctDNA) analysis in high-risk early stage breast cancer patients to monitor and predict response to neoadjuvant therapy and outcome in the I-SPY 2 TRIAL**

#2 Detection of circulating tumor cells (CTC) in blood and disseminated tumor cells (DTC) in bone marrow at surgery identifies breast cancer patients (pts) with long-term risk of distant recurrence and breast cancer-specific death

#3 MRI detection of residual disease following neoadjuvant chemotherapy (NAC) in the -SPY 2 TRIAL

#4 Sequencing of mutational hotspots in the PIK3CA gene of circulating tumor cells (CTCs) from metastatic breast cancer patients

#5 Overcoming drug resistance due to tumor heterogeneity based on single-cell transcriptomics

#6 Mapping phospho-catalytic dependencies of therapy-resistant tumors reveals new actionable vulnerabilities

#7 Predicting Risk of a Subsequent Invasive Event in Patients Diagnosed with DCIS by Assessing Vascular Phenotype

#8 Effect of corrections for image distortion and gradient nonlinearity on longitudinal DTI tumor metrics in breast cancer patients receiving chemotherapy

#9 The multiplexed-Immunohistochemical analysis of immune cell activities in cancer tissues.

#10 Accuracy of MRI after neoadjuvant therapy for invasive lobular carcinoma of the breast.

#11 GeneXpert® Breast Cancer STRAT4 Assay for Analysis of Breast Cancer Biomarker Status from Fine Needle Aspiration Biopsies in Tanzania: Preliminary Results

***Epidemiology and Population Science***

**#1 Rapid On-Site Evaluation (ROSE) of Breast Masses in Tanzania**

#2 Comparing characteristics of patients who fill out online surveys before visits with patients who fill out surveys in-clinic with staff assistance at the UCSF breast screening clinic

#3 Personalized Breast Cancer Screening in a Population-based Study: Women Informed to Screen Depending On Measures of Risk (WISDOM)

#4 Precision Genomics in the Population Health Context: Preliminary Findings from an Embedded ELSI Study of a Risk-Based Breast Cancer Screening Trial

#5 Tobacco Exposure and Breast Cancer in the Athena Breast Health Network

#6 Bridging the gap between genetic research and clinical care: examining the impact of identifying women recommended for risk-reducing strategies by incorporating common genetic variants into a breast cancer risk model

#7 BRCA Challenge: BRCA Exchange as a global resource for variants in BRCA1 and BRCA2

#8 Advocating for Diversity in the WISDOM Breast Cancer Screening Study

#9 Improving Access to Genetic Testing for Breast Cancer Patients: Feasibility of Genetic Testing Station Model to Expedite Testing

#10 Exposure to Phthalates and Risk of Breast Cancer: the Multiethnic Cohort Study

#11 Conceptual Model of Transdisciplinary Science - Advocacy Collaboration for Physical Sciences-Oncology in Breast Density, Biomarker Discovery, and Emerging Therapeutics

#12 Development and Upcoming Pilot of a Personalized, Online Prevention Decision Aid for Breast Cancer Risk Reduction in the WISDOM Study

#13 Factors and risk thresholds characterize the women who use chemoprevention

***Molecular and Cellular Biology***

#1 Lineage-specific epigenetic clocks and increased risk for age-related breast cancer

#2 Physical mechanisms for oncogene-induced breakdown in mammary tissue structure during cancer progression

#3 RNA processing and heat shock proteins are over-expressed in breast tumor compared to normal breast tissue

#4 Host irradiation promotes aggressive tumors by affecting anti-tumor immunity

**#5 Inflammation promotes tumor aggression by stimulating collagen crosslinking and stromal stiffening**

#6 Altered fatty acid trafficking machinery permits elevated fatty acid oxidation in triple-negative breast cancer

#7 BRM loss promotes tumor progression through extracellular matrix remodeling and elevated mammary epithelial stem/progenitor activity

#8 Organoid D2B (Disease to Biology) at Parnassus

*This retreat is supported by: an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Inc., UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103) and unrestricted funds, AstraZeneca and TerSera.*

# Therapeutics and Clinical Trials #4 – BEST THERAPEUTICS AND CLINICAL TRIALS POSTER

## TGFβ inhibition sensitizes breast cancer brain metastasis tumors to radiation treatment

*Alba Gonzalez-Junca, Luis D. Borrero-Garcia, Denis Beckford Vera, Henry Van Brocklin, Benjamin Franc and Mary Helen Barcellos-Hoff*

*Department of Radiation Oncology and Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA, USA*

Presenting Author: Luis D. Borrero Garcia, PhD
Radiation Oncology
luis.borrerogarcia@ucsf.edu

**Abstract**
Breast cancer brain metastases (BCBM) are associated with poor prognosis and limited therapeutic options. Current efforts focus on developing approaches to improve response to radiation therapy (RT) to test whether inhibition of transforming growth factor beta (TGFβ) improves response of brain adapted (BrA) breast cancer to radiation therapy. The rationale for this comes from previous studies that showed that TGFβ is activated in irradiated tissue affecting the composition of the tumor microenvironment and enhancing the ability of tumor cells to survive DNA damage. We first image TGFβ activity in situ using fresolimumab (GC1008), the humanized 1D11 TGFβ neutralizing antibody, radiolabeled with $^{89}$Zr for PET-CT imaging ($^{89}$Zr-fresolimumab). Mice harboring irradiated (15 Gy) 4T1-BrA flank tumors displayed a heightened PET/CT signal compared to un-radiated tumors. We collected irradiated and non-irradiated tumors and perform dual immunofluorescence staining for active TGFβ and phospho-SMAD2. We found TGFβ intensity correlated with the radioactivity of each tumor, which shows specificity of $^{89}$Zr- fresolimumab to detect TGFβ activity in vivo. Next, we tested if inhibition of TGFβ improves response of 4T1-BrA intracranial tumor models to RT. Tumor growth was quantified by measuring bioluminescence (BLI) using IVIS-Xenogen. Image-guided radiation therapy using an Xstrahl small animal radiation research platform and Muriplan planning software was used to deliver a single dose of 10 Gy (sRT) or 5 daily fractions of 6 Gy (fRT). Murine TGFβ neutralizing monoclonal antibody, 1D11, was administered i.p. and mice were monitored by BLI and physical symptoms. Combine treatment with 1D11 and RT led to an increase in median survival compared to RT alone using fRT (49 vs 31 days) or sRT (41 vs 33 days). fRT eliminated tumors in 4/9 mice whereas sRT eliminated 2/12. Double treated mice had similar response by fRT (3/8), but increased with sRT (5/13). Mice that showed complete rejection of tumor were re-challenged with subcutaneous injections of the same tumor cells. Re-challenge showed that only sRT double-treated 4T1-BrA rejected newly tumors. Effective intracranial control of BCBM was achieved by RT and TGFβ inhibition of intracranial tumors and subsequent rejection of tumor re-challenge indicates effective intracranial tumor control can elicit immune memory.

*This retreat is supported by: an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Inc., UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103) and unrestricted funds, AstraZeneca and TerSera.*

# Detection and Biomarkers #1 – BEST DETECTION AND BIOMARKERS POSTER

## Personalized serial circulating tumor DNA (ctDNA) analysis in high-risk early stage breast cancer patients to monitor and predict response to neoadjuvant therapy and outcome in the I-SPY 2 TRIAL

*Authors: 1.Mark Jesus M Magbanua mark.magbanua@ucsf.edu[1], 2.Lamorna Brown-Swigart lamorna.swigart@ucsf.edu[1], 3.Gillian L Hirst gill.hirst@ucsf.edu1, 4.Christina Yau cyau@buckinstitute.org[1], 5.Denise Wolf denise.wolf@ucsf.ed , 6.Aye Aye Ma ayeaye.ma@ucsf.ed , 7.Elizabeth Bergin elizabeth.bergin@ucsf.edu[1], 8.Sara Venters sara.venters@ucsf.edu[1], 9.Himanshu Sethi hisethi@natera.com[2], 10.Hsin-Ta Wu hwu@natera.com[2], 11.Raheleh Salari rsalari@natera.com[2], 12.Tony Tin ttin@natera.com[2], 13.Sarah Sawyer ssawyer@natera.com[2], 14.Maggie Louie mlouie@natera.com[2], 15.Bernhard Zimmermann bzimmermann@natera.com[2], 16.Cheng-Ho Jimmy Lin jlin@natera.com[2], 17.Jonathan Keats jkeats@tgen.org[3], 18.Winnie S Liang wliang@tgen.org[3], 19.Lori Cuyugan lcuyugan@tgen.org[3], 20.Daniel Enrique DEnriquez@tgen.org[3], 21.Debasish Tripathy DTripathy@mdanderson.org[4], 22.Amy Jo Chien jo.chien@ucsf.edu[1], 23.Andres Forero aforero@uab.edu[7], 24.Angela DeMichele angela.demichele@uphs.upenn.edu6, 25.Minetta Liu liu.minetta@mayo.edu5, 26.Amy L Delson amyldelson@gmail.com[1], 27.Smita Asare smita.asare@quantumleaphealth.org[1], 28.Laura Esserman laura.esserman@ucsf.edu1, 29.Laura van't Veer laura.vantveer@ucsf.edu1 and 30.I-SPY 2 Consortium ispy2dapc@quantumleaphealth.org[1].*

*Institutions: [1]University of California San Francisco, San Francisco, California, United States; [2]Natera Inc, San Carlos, California, United States; [3]TGEN, Phoenix, Arizona, United States; 4MD Anderson Cancer Center, Houston, Texas, United States; [5]Mayo Clinic, Rochester, Minnesota, United States; [6]University of Pennsylvania, Philadephia, Pennsylvania, United States and 7University of Alabama, Birmingham, Alabama, United States.*

Presenting Author: Mark Jesus Magbanua, PhD
Laboratory Medicine, Van't Veer Laboratory
mark.magbanua@ucsf.edu

**Abstract**

Body: ctDNA analysis offers a non-invasive approach for monitoring response and resistance to treatment. Serial ctDNA testing during neoadjuvant therapy (NAT) may provide early indicators of emerging resistance and disease progression. In this study, we analyzed ctDNA from high-risk early breast cancer patients who received NAT and definitive surgery in the I-SPY 2 TRIAL (NCT01042379). We hypothesize that (1) assessment of ctDNA levels early in treatment will improve the performance of molecular and imaging-based predictors of pathologic complete response (pCR) to NAT; and (2) levels of ctDNA after NAT are associated with residual cancer burden and recurrence [distant recurrence free survival (DRFS)].

Methods: ctDNA analysis was performed in 84 high-risk stage II and III breast cancer patients randomized to neoadjuvant investigational agent (n=52), AKT inhibitor MK-2206 (M) in combination with paclitaxel (T) followed by doxorubicin and cyclophosphamide (AC) (M+T->AC), or standard-of-care (T->AC) (n=32). HER2+ patients also received trastuzumab (H).

Serial plasma was collected before NAT (T0), early treatment (3 weeks, T1), between regimens (12 weeks, T2), and after NAT prior to surgery (T3). Mutational profiles derived from pretreatment tumor biopsy and normal matched DNA whole exome sequencing were used to design personalized assays targeting 16 patient-specific somatic variants to detect ctDNA in serial plasma.

*This retreat is supported by: an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Inc., UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103) and unrestricted funds, AstraZeneca and TerSera.*

Results: Of the 84 patients in this study, 43% were HR-/HER2- (TNBC), 35% HR+/HER2-, and 23% HER2+. In total, 74% (61 of 83), 35% (28 of 79), 14% (9 of 65), and 8% (5 of 61) were positive for ctDNA at timepoints T0, T1, T2, and T3, respectively. At T0, ctDNA positivity and levels (average number of mutant molecules detected per mL) were significantly associated with increased tumor burden (by clinical and MRI examination), more aggressive tumor biology (as reflected in higher Mammaprint scores and grade) and subtype (HER2+ and TNBC). In some cases, the dynamics of ctDNA levels during neoadjuvant therapy reflected changes in tumor responses as measured by MRI. Twenty-seven percent (27%) of the 84 patients achieved a pCR and all patients who were ctDNA-positive at T3 (n=5) did not achieve a pCR. For patients who are ctDNA+ at T0, early clearance of ctDNA predicted pCR (OR=3.38; LR p=0.040) and RCB 0/1 (OR=3.56; LR p=0.028). The presence of ctDNA after neoadjuvant therapy was significantly associated with poor distant recurrence-free survival (HR: 7.42; 95% CI,1.66-33.21; p=0.002) and event-free survival (HR: 9.11; 95% CI, 2.44-34.06; p=0.0001).

Conclusions: Our study provides a platform to evaluate the clinical significance of ctDNA for serial monitoring of response to NAT. Accurate and early response prediction by highly sensitive ctDNA analysis can facilitate a timely and judicious change in treatment to improve patients' chances of achieving a pCR. Finally, personalized ctDNA testing may complement imaging and pathologic evaluation of tumor response to fine-tune pCR as a surrogate endpoint for improved DRFS and EFS.

*This retreat is supported by: an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Inc., UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103) and unrestricted funds, AstraZeneca and TerSera.*

# Epidemiology and Population Science #1 – BEST EPIDEOMOLOGY AND POPULATION SCIENCE POSTER

## Rapid On-Site Evaluation (ROSE) of Breast Masses in Tanzania

*Asteria Kimambo MD[1], Godfrey S. Philipo MD MPH[1], Ronald Balassanian MD[2], Beatrice P Mushi MD MPH [1], Msiba Selekwa Nyeriga MD[1], Britt-Marie Ljung MD[2], Katherine Van Loon MD MPH[2], Elia Mmbaga MD PhD[1], Edda Vuhahula DDS PhD[1]*, Dianna Ng MD[2]**

**co-senior authors*
*Affiliation: [1]Muhimbili University of Health and Allied Sciences, [2]University of California, San Francisco*

Presenting Author: Dianna Ng, MD; co-presenter Ronald Balassanian, MD
Pathology
Dianna.Ng@ucsf.edu and Ronald.Balassanian@ucsf.edu

**Abstract**
Introduction: Fine needle aspiration biopsy (FNAB) is a rapid, minimally invasive and cost-effective technique ideal for low resource settings. Breast FNAB has high accuracy when performed by a trained operator. FNAB can be combined with rapid on-site evaluation (ROSE) to assess adequacy, triage for ancillary testing, and determining preliminary diagnoses. Feasibility and accuracy of ROSE in determining cellular adequacy and preliminary diagnoses in a low-resource setting was evaluated at an FNA Clinic at a national hospital in Dar es Salaam.

Methods: IRB approval was obtained from all participating institutions. Adult patients with a breast mass who presented to the clinic were enrolled in the study with informed consent from Jan 2018 to present. FNAB was performed by one author (AK) who received intensive training in FNAB at the affiliated institution in the United States. ROSE using toluidine blue stain on alcohol-fixed smears was performed to determine the adequacy, and categorized as low, moderate or high cellularity. Preliminary diagnoses, categorized as benign or malignant, were compared to the final diagnoses.

Results: A total of 88 patients were enrolled (median age 49 years, range 23-78). All cases were adequate in cellularity. ROSE was malignant in 63 (72%) and benign in 25 (28%) patients. The concordance between ROSE and final diagnosis was 96% (85/88). The 3 discordant cases were malignant at ROSE, but diagnosed as benign on final review of the Pap stained slides. Diagnoses included fat necrosis, proliferative fibrocystic change, and benign breast tissue. There were 28 cases with 1 pass, 24 with 2 passes, 30 with 3 passes and 6 with 4 passes. All malignant cases had at least one pass that had moderate or high cellularity.

Conclusion: ROSE is a simple, cost-effective method to determine adequacy and cellularity in a low-resource setting. With training, ROSE can be used to determine preliminary diagnoses with high accuracy. Accurate ROSE allows for triage for ancillary testing, optimizing the use of scarce resources for patients when indicated while reducing inadequate FNAB rates and the need for repeat biopsies, and to help identify patients for specialized cancer care.

*This retreat is supported by: an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Inc., UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103) and unrestricted funds, AstraZeneca and TerSera.*

# Molecular and Cellular Biology #5 – BEST MOLECULAR AND CELLUALR BIOLOGY POSTER

## Inflammation promotes tumor aggression by stimulating collagen crosslinking and stromal stiffening

*Allison P. Drain, Ori Maller, Alexander S. Barrett, Signe Borgquist, Brian Ruffell, Pham T Thanh, Tina Gruosso, Hellen Kuasne, Johnathon N. Lakins, Yoshihiro Yui, Irene Acerbi, Janna K. Mouw, J. Matthew Barnes, Travis Nemkov, Aastha Chauhan, Jessica Gruenberg, Aqsa Nasir, Jonas Manjer, Olof Bjarnadottir, Catharina Hagerling, Zena Werb, Peter Kabos, Yunn-Yi Chen, E. Shelley Hwang, Andrew C. Nelson, Morag Park, Lisa M. Coussens, Kirk C. Hansen, and Valerie M. Weaver*

Presenting Author: Allison Drain
Bioengineering, Weaver Laboratory
adrain@berkeley.edu

**Abstract**
Collagen deposition and stiffening accompany malignancy, compromise treatment and promote tumor aggression. Clarifying the molecular nature of and the factors that regulate the stiffened collagenous extracellular matrix in tumors has the potential to identify biomarkers to stratify patients for therapy, and to identify therapeutic interventions to improve outcome. Using an optimized, analytical method to profile lysyl hydroxylase- and lysyl oxidase-mediated collagen crosslinks we quantified the greatest number of collagen crosslinks in biopsies of the more aggressive human breast cancer subtypes with the stiffest stroma. The stiffest and most aggressive breast cancers also harbored the highest number of tumor-suppressive macrophages, whose therapeutic ablation not only reduced metastasis in the PyMT mouse model of mammary cancer, but also concomitantly inhibited collagen crosslinking and stromal stiffening. Neither epithelial knockout of HIF1α, a potent inducer of collagen crosslinking enzymes, nor epithelial-targeted expression of the crosslinking enzyme lysyl oxidase, had any impact on collagen crosslinking in endogenous PyMT mammary tumors, whereas stromal cell targeting did. Consistently, the micro-dissected stromal cells, and not the tumor epithelium, in the more aggressive human breast tumor tissue, expressed the highest level of collagen crosslinking enzymes that correlated significantly with the level of infiltrating tumor macrophages. Indeed, immunohistochemical analysis of a large cohort of breast cancer patient biopsies confirmed that stromal, but not epithelial, collagen crosslinking enzyme expression correlated significantly with poor patient outcome and disease specific mortality. The findings provide a compelling link between tissue inflammation, stromal cell-mediated collagen crosslinking and stiffening and tumor aggression.

*This retreat is supported by: an educational grant from Daiichi Sankyo, Inc., Puma Biotechnology, Inc., UCSF Helen Diller Family Comprehensive Cancer Center support grant (P30CA82103) and unrestricted funds, AstraZeneca and TerSera.*