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

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Abstract
The explosion in new treatment options targeting immune checkpoints, HER signaling, DNA repair deficiency, AKT, and other pathways calls for updated breast cancer subtypes beyond HR and HER2 status to predict which patients will respond to which treatments. Here we leverage the I-SPY 2 TRIAL biomarker program over the past 8 years across 10 treatment arms to elucidate a minimal set of biomarkers that may improve response prediction in a modern treatment context, and to investigate which new patient phenotypes are identified by these response-predictive biomarkers.

Methods: 986 patients were considered in this analysis. Treatments included paclitaxel alone (or with trastuzumab (H) in HER2+) or combined with investigational agents: veliparib/carboplatin (VC); neratinib; MK2206; ganitumab; ganetespib; AMG386; TDM1/pertuzumab (P); H/P; and pembrolizumab (Pembro). 24 prospectively defined, mechanism-of-action and pathway-based expression and phospho-protein signatures/biomarkers assayed from pre-treatment biopsies were previously found to be predictive in a particular agent/arm in pre-specified analysis. Here we evaluate these biomarkers in all patients. We assessed association between each biomarker and response in the population as a whole and within each arm and HR/HER2 subtype using a logistic model. To identify optimal dichotomizing thresholds for select biomarkers, 2-fold cross-validation was repeated 500 times. Our analysis is exploratory and does not adjust for multiplicities.

Results: Our initial set of 24 predictive biomarkers reflects DNA repair deficiency (n=2), immune activation (n=7), ER signaling (n=2), HER2 signaling (n=4), proliferation (n=2), phospho-activation of AKT/mTOR (n=2), and ANG/TIE2 (n=1) pathways, among others. Biomarkers reflecting similar biology are correlated and cluster together. We make use of this correlation structure to reduce the dimensionality of the biomarker set to five

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predictive signals: proliferation, DNA repair deficiency (DRD), immune-engaged (Immune+), luminal/ER (lum), and HER2-activated. These biomarkers, when dichotomized, identify patient groups with differential predicted sensitivities to I-SPY 2 agents and are present at different proportions within receptor subtypes. For instance, in the HER2- subset, Immune+/DRD+ patients are predicted sensitive to both VC and Pembro, and account for 39% of TN, but only 12% of HR+HER2-. On the other end of the spectrum, only 17% of TN are Immune-/DRD-, compared to the majority (56%) of HR+HER2-. There are also subsets of patients positive for only one marker. For the HER2+ subset, 67% are HER2-activated+, and 25% lum+; of these HER2-activated+ patients are more likely to be Immune+ (44%), vs 23% in lum+. HER2-activated+/Immune+ patients have higher predicted sensitivity to HER2-targeted agents than lum+ or Immune- patients.
In all, these molecular phenotypes predict sensitivity to one or more I-SPY 2 investigational agents for 75% of the ~ 1000 patients.

Conclusion: Molecular phenotypes reflecting proliferation, immune engagement, HER2-activation, luminal/ER-signaling, and DNA repair deficiency may provide a roadmap to guide treatment prioritization for emerging therapeutics.

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Therapeutics and Clinical Trials #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

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Abstract

Background: While pathological complete response (pCR) is associated with an improved event-free (EFS) and distant recurrence-free survival (DRFS) with standard, approved treatment in the neoadjuvant therapy of breast cancer, it is unknown whether this would hold for investigational agents. We tested this hypothesis in nine investigational arms and controls in the ongoing, adaptive, phase 2 platform trial, I-SPY2.

Methods: Women with breast tumors > 2.5 cm were adaptively randomized to better performing agents compared with control therapy within molecular subtypes, using HER2, hormone-receptor and the 70-gene assay. Hormone receptor +/HER2-/70-gene low-risk tumors were excluded. EFS and DRFS were evaluated by pCR status within subtypes. Hazard ratios (HR) were based on Cox proportional hazards regression. Associations between pCR and EFS were analyzed by therapeutic arm using Bayesian and hierarchical modeling with adjustments for molecular subtype.

Results: The analysis was restricted to patients who had at least 2 years of follow-up, with 741 patients (of over 1200 randomized) eligible for analysis; median follow-up was 2.7 years. Three-year EFS and DRFS for patients achieving pCRs were 94% and 95%, respectively. For pCR versus non-pCR, mean HR=0.20 for both endpoints, regardless of modelling method, with the 95% probability interval ranges from 0.1-0.35.. HRs were similarly low within subtypes and specific treatment arms. Even when assigned treatments were not superior to control, achieving a pCR on any treatment arm resulted in significantly lower HR compared to non-pCR.

Conclusion: Achieving pCR after neoadjuvant chemotherapy for women at high risk of early recurrence predicts an excellent outcome, regardless of subtype, even with the addition of investigational drugs, with 94% of patients remaining disease-free at 3 years. pCR is an early endpoint that can serve to support individualized de-escalation or escalation strategies for drug development trials designed to optimize outcomes. Results by treatment arm will be shown.

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Therapeutics and Clinical Trials #3

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

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Abstract

Background: The 80-gene BluePrint (BP) signature can be used to classify breast cancers based on their expression profiles into 3 subtypes: Luminal, HER2, and Basal; previous studies show BP subtypes predict response to neoadjuvant chemotherapy. I-SPY 2 is a multicenter Phase 2 platform trial evaluating novel agent/combinations added to standard chemotherapy within Hormone Receptor (HR)/HER2/MammaPrint (MP) defined signatures. We have previously observed that, in the I-SPY 2 TRIAL, HR+HER2+ BP HER2-type™ patients are more likely to respond to HER2-targeted agents/combinations than HR+HER2+ BP Luminal-type™ patients. In this study, we evaluated BP subtype as a predictor of response among HR+HER2- patients in the I-SPY 2 TRIAL.

Methods: The BluePrint signature was applied to assign subtypes for 981 I-SPY 2 patients, 375 of whom are HR+HER2- (and randomized to one of 7 experimental therapy or control arms). We compared the expression levels of ER, PR and basal-type keratins (KRT5/14/17) between BP subtypes using a Wilcoxon rank sum test. Association between BP subtypes and MP (High1/High2) class are used in I-SPY2 randomization; pathological complete response (pCR) was evaluated with Fisher™ Exact test and logistic regression adjusting by treatment arm. A Bayesian hierarchical logistic modeling estimated pCR rates as a function of BP subtypes within treatment arms. Our statistics are descriptive rather than inferential and do not adjust for multiplicities of biomarkers outside this study.

Results: While the majority of HR+HER2- patients (266/375) are BP Luminal, 29% (108/375) are BP basal-type. As expected, HR+HER2- BP Luminal patients have higher ER/PR and lower basal keratins expression levels, when compared to HR+HER2- BP Basal patients ($p<0.0001$). In addition, BP subtype is associated with MP class, where 77% of HR+HER2- BP Basal patients are MP High2 class, compared to only 9% of HR+HER2- BP Luminal patients. Across all arms, HR+HER2- BP basal-type patients is more likely to achieve a pCR when compared to BP luminal patients (Odds Ratio: 4.41, $p<0.0001$), with similar association observed in a treatment-arm adjusted model (Odds Ratio: 4.98, $p<0.0001$). Within treatment arms, the estimated pCR rates among HR+HER2- BP Basal patients ranged from 29%-41%, compared to 7%-17% in HR+HER2- BP Luminal patients.

Conclusion: Our findings suggest that the BP basal signature identifies a subset of HR+HER2- patients who are more likely to respond to neoadjuvant chemotherapy. The overlap between BP-basal and MP2 class suggests that different predictive signatures may identify similar sets of responsive patients. These findings will aid in guiding prioritization of targeted agents when the goal is to optimize the chance of pCR for patients.

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

TGFβ inhibition sensitizes breast cancer brain metastasis tumors to radiation treatment

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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.

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Therapeutics and Clinical Trials #5

Chemically Designing Therapeutic Enzymes That Bind to Breast Cancer

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Abstract
Our goal is to decrease chemotherapy side effects by making a therapeutic enzyme that finds a tumor and converts a nontoxic molecule, a prodrug, to a toxic drug only inside the tumor. This therapeutic enzyme is called an antibody-enzyme conjugate, and is composed of two proteins that are chemically connected. The antibody sticks specifically to the surface of HER2+ breast cancer cells, and the enzyme cytosine deaminase transforms a safe prodrug to the toxic drug 5-fluorouracil. Previous attempts to make antibody-enzyme conjugates were limited by the way the two proteins were connected that resulted in a heterogeneous mixture. We independently control the number of antibody and enzyme domains by using site-specific covalent bonds to link each domain. We synthesized homogeneous antibody-enzyme conjugates with varying numbers of domains and observed cytotoxic activity for cells that expressed the HER2 receptor. We expect the ability to generate homogeneous antibody conjugates will also benefit multispecific antibodies and multivalent signaling molecules.

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Therapeutics and Clinical Trials #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

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Abstract

Background: Addition of the cyclin dependent kinase 4/6 inhibitor (CDK4/6i) palbociclib to endocrine therapy in the first and later line settings significantly improves progression free survival (PFS) in patients with HR+ MBC. The primary toxicity is neutropenia without an increase in febrile neutropenia. TBCRC035 explored rates of neutropenia in patients who had received prior chemotherapy for MBC with 2 dose levels of palbociclib, and correlated changes in retinoblastoma protein phosphorylation (pRB) and Ki67 expression in proliferating keratinocytes and tumor with response.

Methods: TBCRC035 is a 1:1 randomized multicenter phase II study evaluating palbociclib at either 125 or 100 mg in combination with physician choice fulvestrant or tamoxifen. Eligible patients (pts) with HR+ MBC had received $\geq$1 but $\leq$3 lines of chemotherapy for MBC, any number of prior hormone therapies, and were naïve to CDK4/6i. The primary endpoint was grade 3/4 neutropenia; secondary endpoints included response, safety/tolerability, inhibition of pRB and change in Ki67 in skin and tumor at day 14-21 of treatment compared to baseline. FFPE sections of skin punch and tumor biopsies obtained before and on treatment were stained using antibodies to Ki67, total RB, and phospho-RB-S780 using BOND polymer red detection. Stained slides were scanned into the Aperio image analysis platform; the percentage of marker positive cells and H-score was determined.

Results: 70 pts were enrolled (fully accrued); 35 randomized to 100 vs 125 mg of palbociclib respectively; data for the last 3 pts on the 125 mg arm is pending. Grade 3/4 neutropenia was more common in the 125 mg vs the 100 mg arm (56 vs 34%); dose adjustments for adverse events (AEs) occurred in 47 vs 43%, 4 vs 0 pts discontinued treatment due to AEs. Grade 3 febrile neutropenia was rare (1 patient each arm). Median duration of treatment was 5.2 vs 7.2 months. Response data and correlation with changes in pRB and Ki67 expression in skin and tumor by treatment arm will be reported.

Conclusion: In pts with prior chemotherapy for HR+ MBC, treatment with 100 mg of palbociclib in patients is associated with a lower rate of $\geq$ grade 3 neutropenia compared to 125 mg. Correlation of response by dose with pRB and Ki67 has the potential to inform palbociclib dosing and reduce toxicity for pts with HR+ MBC.

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Therapeutics and Clinical Trials #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)

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Abstract

Background: CALGB 40503 randomized post-menopausal patients with HR+ MBC to receive letrozole (Let) alone or Let with bevacizumab (Bev) as first-line therapy. The addition of Bev to Let prolonged progression-free survival (PFS), but not overall survival (OS) (Dickler JCO 2016). We performed a correlative study to assess the prognostic and predictive value of CTCs in this patient population.

Methods: Blood samples were collected prior to initiation of treatment. CTCs were enumerated using the US Food and Drug Administration-cleared CellSearch assay, and samples with 5 or more CTCs per 7.5 mLs of blood were considered positive. Correlation of CTCs with progression-free survival (PFS) and overall survival (OS) were assessed using Cox regression analysis. The median follow-up was 39 months (mos).

Results: Of 343 pts treated, 294 had CTC data and were included in this analysis. Original study results that showed improved PFS (HR = 0.75; 95% CI: 0.59-0.96) but not OS (HR = 0.87; 95% CI: 0.65-1.18) in pts receiving Let+Bev compared to Let were recapitulated in this subset. In multivariable analysis, CTC+ pts (31%) had significantly reduced PFS (HR = 1.49; 95% CI: 1.12-1.97) and OS (HR = 2.08; 95% CI: 1.49-2.93) compared to CTC- pts. Moreover, CTC+ pts who did not receive Bev had worse PFS (HR = 2.31; 95% CI: 1.54-3.47) and OS (HR = 2.64; 95% CI: 1.59-4.40) (Table 1). CTC+ pts who received Bev had numerically longer median PFS (18.0 vs. 7.0 mo) and OS (33.6 vs. 27.1 mo) compared to CTC+ pts with no Bev; however, tests for interaction between CTC status and Bev (yes vs. no) were not statistically significant for PFS (p=0.70) or OS (p=0.84).

Conclusions: CTCs were highly prognostic in this study involving addition of Bev to first-line Let in postmenopausal HR+ MBC. Further research to determine the potential predictive value of CTCs in the setting of both metastatic disease and early breast cancer is warranted.

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Table 1. Survival in HR+ MBC pts receiving Let or Let+Bev stratified by CTC status.

	Total	Events	Median survival in mo (95% CI)	Adjusted Hazard Ratio (95% CI)	Adjusted Likelihood-Ratio p-value
PFS					0.0012
CTC-: Let+Bev	108	70	18.4 (15.0-23.5)	1.0	
CTC-: Let	94	74	14.7 (11.4-18.9)	1.44 (1.02-2.02)	
CTC+: Let+Bev	46	42	18.0 (13.6-23.7)	1.44 (0.98-2.13)	
CTC+: Let	46	38	7.0 (2.8-10.9)	2.31(1.54-3.47)	
OS					0.0003
CTC-: Let+Bev	108	35	49.1 (42.4-NE)	1.0	
CTC-: Let	94	44	45.0 (40.1-50.1)	1.29 (0.82-2.03)	
CTC+: Let+Bev	46	34	33.6 (26.6-40.0)	2.20 (1.37-3.55)	
CTC+: Let	46	28	27.1 (20.6-36.1)	2.64 (1.59-4.40)	

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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

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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.

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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.

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Detection and Biomarkers #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

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Abstract
Purpose: We examined the prognostic impact of CTCs and DTCs detected at the time of definitive surgery in pts diagnosed with early breast cancer (EBC).

Methods: Blood and bone marrow samples from 742 treatment-naive EBC pts, not eligible for neoadjuvant therapy, were collected immediately prior to surgery. 87% were hormone receptor (HR)-positive, and 71% were node-negative. DTCs (n=584) were enumerated using an EPCAM-based method involving immunomagnetic enrichment and flow cytometry (IE/FC). CTCs were enumerated either by IE/FC (n=288) or CellSearch (n=380). Optimal cutoffs for CTC-/DTC-positivity were selected using Monte-Carlo cross validation. Multivariate Cox regression analysis was performed to determine correlation between levels of CTCs/DTCs vs. distant recurrence-free survival (DRFS) and breast cancer-specific survival (BCSS). The overall median follow-up was 7.1 years for DRFS and 9.1 years for BCSS, but extended up to 13.3 years in subset analyses (Table 1).

Results: CTC-positivity by CellSearch was associated with HER2-positivity (Fisher p=0.01). Using optimized cutoffs in multivariate analyses, we found that CTC-positive pts by CellSearch had a statistically significant increased risk of distant recurrence (HR 4.93, p=0.0067). Moreover, pts who were CTC-positive by IE/FC had a statistically significant increased risk of breast cancer-specific death (HR=3.54, p=0.0138). DTC status, by itself, was not prognostic; however, when combined with CTC status by IE/FC (n=273), positive detection for both (CTC+DTC+) was significantly associated with increased risk of distant recurrence (HR=3.09, p=0.0270) and breast cancer-specific death (HR=4.55, p=0.0205).

Conclusions: We demonstrate the impact of quantitative evaluation of CTCs and DTCs by IE/FC. Our large single institution dataset, in which CTCs and DTCs have been contemporaneously quantitated, has the longest patient follow-up. Simultaneous detection of CTCs and DTCs at the time of definitive surgery in treatment naive EBC pts is an independent prognostic factor associated with increased long-term risk of distant recurrence and death due to breast cancer. Given the lack of early endpoints for low-risk patients, liquid biopsy may be an important consideration for future studies.

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Detection and Biomarkers #3

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

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Abstract

Body: Background: Detecting residual disease accurately using MRI after NAC to identify both responders and non-responders is essential for deescalating therapy or redirecting patients to more effective treatment. The purpose of this study is to determine if the combination of longest diameter (LD) and functional tumor volume (FTV) from dynamic contrast enhanced (DCE) MRI is superior to FTV alone or LD alone for assessing treatment response after neoadjuvant therapy in breast cancer patients.

Methods: Data from patients in the graduated drug arms of the ISPY 2 trial were included in the analysis. Both LD and FTV were assessed using DCEMRI after neoadjuvant therapy. LD was measured by the site radiologist as the longest dimension of the enhanced area on early post-contrast images. Functional tumor volume (FTV) was assessed as the sum of voxels with enhancement above specific thresholds within the pre-defined region-of-interest (ROI). A linearized variable was derived to represent the combination of FTV and LD. The area under the receiver operating characteristic curve (AUC) was used to evaluate the assessment of treatment response, pathologic complete response (pCR), defined as no invasive disease in the breast and lymph nodes, and in-breast pCR, defined as no invasive disease in the breast only. The analysis was performed in the full cohort and in breast cancer subtype defined by hormone receptor status and HER2 status.

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Results: Among the patient cohort of N=675 with FTV and LD, 247 (37%) did and 428 (41%) did not achieve pCR after neoadjuvant therapy. pCR rates varied among HR/HER2 subtypes (HR+/HER2: 19%; HR+/HER2+: 38%; HR/HER2+: 71%; HR/HER2 (triple negative, TN): 43%). In-breast pathologic complete response rates were slightly higher in each group (full: 41%; HR+/HER2: 23%; HR+/HER2+: 43%; HR/HER2+: 72%; HR-/HER2: 49%). Higher AUCs were observed in all patient groups using the combined variable. AUC of 0.79 (95% CI: 0.77, 0.81) was observed for the combined variable to assess pCR in the full cohort. AUCs varied from 0.69 to 0.86 among HR/HER2 subgroups (HR+/HER2: 0.69; HR+/HER2+: 0.74; HR/HER2+: 0.86; HR-/HER2: 0.80), with no difference in assessing pCR or in-breast pCR. The performance is best for the HR subtypes.

Conclusions: Both FTV and LD can be used in the assessment of invasive disease residual after neoadjuvant therapy. The combined variable of FTV and LD achieved highest AUCs, compared to using individual variable alone. Tools to improve performance in the HR+ subsets are underway.

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Detection and Biomarkers #4

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

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Abstract
Background: Mutations in the PIK3CA gene encoding for the phosphatidylinositol 3-kinase (PI3K) enzyme have been documented in different types of cancers. For example, PIK3CA is mutated in approximately 36% of primary breast tumors. Three common sites of oncogenic point mutations within two mutation "hotspots" of the PIK3CA gene have been observed on codons 542 and 545 of Exon 9, and codon 1047 of Exon 20. In this study, we examined the incidence of PIK3CA mutations in CTCs from metastatic breast cancer patients.

Methods: Blood samples were collected from 320 metastatic breast cancer patients undergoing treatment in the CALGB 40502 and CALGB 40503 trials. Serial samples were drawn at various time points during therapy. EPCAM-positive CTCs from blood were then isolated using immunomagnetic enrichment followed by fluorescence activated cell sorting (IE/FACS). CD45-positive leukocytes were also collected and served as normal controls. Genomic DNA from cells were subjected to whole genome amplification. Exons 9 and 20 of the PIK3CA gene were amplified via PCR. Amplicons were subjected to Sanger sequencing Evaluable traces from 318 patients were then analyzed for the presence of mutations using BLAST Global Alignment tool.
Results: Of the 318 patients, 94%, 27%, 10%, 11%, 4% had 1 to 5 time points. 56% of patients had CTCs that carried a mutation either in exon 9 or exon 20. The most common non-synonymous mutations observed were E545K and S535F in exon 9, and H1047R and E1012K in exon 20. Novel mutations not previously reported in the Catalogue of Somatic Mutations in Cancer or by The Cancer Genome Atlas were also detected (e.g., exon 9: S553G; exon 20: Y1021D). In some cases, different mutations were observed in CTCs across time points from the same patient.

Conclusions: The PIK3CA gene is commonly mutated in CTCs of metastatic breast cancer patients. CTCs from the same patient may show heterogeneity in PIK3CA mutation status over time. The clinical significance of this observation remains to be elucidated.

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Detection and Biomarkers #5

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

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Abstract
Rare tumor subpopulations have been identified as a potential mode of resistance in cancer, yet the extent to which transcriptional heterogeneity drives altered cell states and drug response in breast cancer is largely unknown. Here we developed a method for systematically identifying upfront combinations to counteract heterogeneity by predicting drug responses based on single-cell RNAseq data. Using the 10X Genomics Chromium™ platform, we profiled the transcriptomes of individual cells across breast cancer cell lines and patient derived xenograft (PDX) models, and obtained single-cell data from a cohort of TNBC patients. Gene-based heterogeneity was assessed by categorizing the captured cells into distinct subpopulations using a combination of tSNE embeddings and clustering algorithms. Co-existing subpopulations were observed in all models tested, revealing widespread heterogeneity at the transcript level.

Recently, our lab developed MAGNETIC (Modular Analysis of Genomic NETworks In Cancer), a computational method to decompose the genomics profiles of breast cancer patients into gene modules using multi-platform -omics data. This approach identified gene modules that are highly reflective of variation between tumors, providing a catalog of molecular programs that can be used to discover clinically relevant biomarkers of response in breast cancers. Analysis of single cells based on pathway-enriched gene modules revealed rare cells enriched for processes known to impact therapeutic response, including a persistent IFN-subpopulation in TNBCs as a potential marker of aggressive disease. We next leveraged a module-drug network to identify determinants of drug sensitivity and applied these biomarkers to predict the response state of individual cells, identify putative resistant subpopulations, and nominate novel drug combinations. Ongoing work towards developing a single-live-cell tracking workflow will provide direct validation of the functional impact of these rare subpopulations and their contribution towards drug response. These results demonstrate the utility of our approach in characterizing, predicting and targeting distinct subpopulations by leveraging scRNAseq data and existing drug response databases to identify new treatment strategies for combating tumor heterogeneity.

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Detection and Biomarkers #6

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

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Abstract
Phosphorylation networks intimately regulate mechanisms of response to therapies. Mapping the phospho-catalytic profile of kinases in cells or tissues remains a challenge. Here, we introduce an innovative high-throughput system we developed to simultaneously measure the enzymatic activity of >100 kinases in cancer cell lines and patient tumor biopsies, using biological peptide targets of kinases as phospho-sensors (publication in final revision in Nature Cell Biology). We will provide examples of how the systematic exploration of phospho-catalytic dependencies of therapy-resistant tumors can help reveal new actionable vulnerabilities across cancer types, including $BRAF^{V600E}$ colorectal cancer, melanoma, and triple-negative breast cancer (TNBC).

Focusing on $BRAF^{V600E}$ metastatic colorectal cancer (mCRC), a disease with extremely poor prognosis and for which targeted therapies have had underwhelming results in trials, we discovered new cooperative mechanisms of intrinsic resistance to BRAF/MEK pathway-targeting drugs. This includes a cell-autonomous, NRTK-relayed, inflammatory program that functions independently of the commonly studied EGFR/RAF-MEK-ERK/PDPK1-AKT1 pathways. This new druggable target significantly reduces tumor burden in a series of patient-representative $BRAF^{V600E}$ mCRC PDX models, systematically outperforms regimens currently in trials, and has no measurable toxicity in combinatorial therapy strategies (manuscript in preparation).

Importantly, our platform also enables to map the phospho-catalytic signatures of resected tumor specimens. This identified RPS6KB1 and PIM1 as novel emerging druggable vulnerabilities predictive of poor outcome in melanoma patients.

Finally, in the context of the adaptive responses of BRCA-mutated TNBC to PARP-targeting therapy and chemotherapy, mapping the kinase activity signatures of laboratory model systems enabled us to find new functional determinants. We are currently testing whether inhibiting these unique sets of hyper-activated signaling pathways may identify druggable 'hot-spots' to avert drug resistance, and potentially improve patients' outcome.

Our results show that therapeutic resistance can be caused by the concerted upregulation of interdependent pathways. Our kinase-activity mapping system is a versatile, scalable strategy that innovates the exploration of actionable kinases for precision medicine.

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Detection and Biomarkers #7

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

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Abstract
Background: Widespread adoption of screening mammography has made ductal carcinoma in situ (DCIS) an increasingly common diagnosis. DCIS is widely viewed as a precursor to invasive breast cancer (IBC) and is nearly universally treated with surgery, radiation and/or hormone therapy. Contrary to the established paradigm, recent evidence suggests that DCIS lesions are biologically heterogeneous and are not uniformly capable of progressing to life threatening IBC. The absence of adequate biomarkers to predict which women diagnosed with DCIS will develop IBC contributes to the overtreatment of a significant number of women.

Methods: In disease-free breast tissue, the capillaries adjacent to mammary epithelial structures highly express the scavenger receptor CD36, whereas larger diameter vessels above the terminal branchpoint highly express the classic endothelial marker CD31 instead. Strikingly, the CD36-expressing vasculature is almost entirely absent from IBCs. Based on this phenotypic difference, we developed a multiplex immunohistochemical assay to determine the proportion of CD36- and CD31-expressing vasculature and evaluate the predictive value of this signature for risk stratification in DCIS. We utilized archival formalin-fixed paraffin-embedded material that was retrospectively collected from patients with known outcome (n=90) diagnosed between 1983 and 1996 and treated by lumpectomy-alone (median follow-up 15 years).

Results: Analysis of this DCIS cohort revealed that among patients (n=25) where the proportion of the total vasculature expressing CD36 was similar to the levels seen in disease-free breast tissues (>75%), only 9% developed IBC during follow-up. In contrast, for those patients (n=29) where the proportion of the total vasculature expressing CD36 was similar to the levels seen in IBC (<25%), 62% developed IBC during follow-up. For those patients (n=36) in the intermediate group (25-75%), 28% developed IBC during follow-up

Significance: This analysis reveals that phenotypic differences in the vasculature surrounding DCIS lesions can stratify patient outcome into low-, intermediate-, and high-risk groups. In contrast to previous assays looking at the prognostic significance of microvessel density alone, this assay provides novel insights into the hierarchical organization of the vascular network and the angiogenic proclivity of its components (interactions between CD36 and its ligand thrombospondin-1 can restrain angiogenesis).

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Detection and Biomarkers #8

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

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Abstract
Introduction: Diffusion tensor imaging (DTI) provides information on tissue cellularity and microstructure. A DTI-derived metric, apparent diffusion coefficient (ADC), has shown promise as a biomarker of breast cancer treatment response. However, standard echo-planar imaging (EPI) DTI is limited by geometric distortions resulting from the susceptibility-induced variation in the B0 field and eddy-currents (ECs) from diffusion-encoding gradients. This distortion occurs in addition to gradient non-linearity (GN) effects which can also affect quantification of DTI-derived metrics. A robust method for correcting geometric distortions in DWI utilizes an extra reverse phase gradient (RPG) acquisition. This correction strategy was shown to improve the accuracy of diffusion tensor imaging (DTI) metrics in a phantom. However, there is little data on the effects of RPG-based correction on the quantification of breast tumor DTI metrics in longitudinal studies of neoadjuvant treatment response. This work evaluated the effects of GN correction and the addition of RPG and EC distortion corrections on 1) DTI metrics in malignant breast tumors measured at two treatment time points and 2) the alignment of tumor regions of interest (ROIs) on DTI and corresponding DCE-MRI

Methods: DTI, with RPG acquisition, and DCE-MRI were acquired on a 1.5T MRI-scanner in 6 breast cancer patients, enrolled in an IRB-approved study, prior to treatment (T0) and after three weeks of therapy (T1). The effects of adding RPG and EC distortion corrections to GN-correction on tumor ADC and FA values were calculated. The alignment between the DTI tumor ROIs (uncorrected and corrected) and DCE-MRI enhancing voxels was assessed using the Dice coefficient.

Results: GNC correction reduced tumor ADC with a significant difference between pre- and post correction values for both T0 and T1. Addition of RPG and EC corrections to GN correction significantly decreased FA at T0 with a smaller decrease seen at T1. Addition of RPG and EC corrections also improved the alignment of DTI and DCE-tumor ROIs as demonstrated by the increase in Dice coefficient and percent of common voxels between DTI and DCE-MRI tumor ROIs.

Discussion: The corrections had significant effects on tumor DTI metrics and improved alignment of DTI and DCE-MRI tumor ROIs.

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Detection and Biomarkers #9

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

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Abstract
The necessity of analyzing multiple biomarkers in the tissue samples have been increasing, and analyzing associations between a tumor and immuno-microenvironment are important task to understanding the cancer progression status before and after anti- cancer treatment. Our pilot study seeks to establish profiling data to capture immune cells and their activities in breast cancer tissues. Here we introduce our optimized tissue analysis utilizing multiplexed immunohistochemistry (mIHC) with a tyramide signal amplification which allows us to visualize up to 7 markers simultaneously. This mIHC assay allows us to detect combinations of: immune cell markers (CD3, CD8, CD20, CD68, CD117, FoxP3), immune checkpoint status markers (PD1, PD-L1, ICOS, IDO1, B7H3, B7H4, B7H5, LAG3, TIM3 and other markers TBD) and additional clinical/pathological markers (e.g. cytokeratins and Ki67). In addition to visualizing each marker, we will report Quantitative Image analysis analyses (QIA) of immune cell types and activities in tissue images. This advanced tissue analysis will prepare for the next stage for deep understanding in cancer progression and will supply a comprehensive map of biomarkers in cancer tissues.

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 #10

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

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Abstract
Invasive lobular carcinoma of the breast (ILC) has higher rates of false negative imaging than invasive ductal carcinoma, and lower rates of neoadjuvant therapy (NAT) use. We evaluated the accuracy of Breast Imaging Reporting And Data System (BIRADS) findings on magnetic resonance imaging (MRI) after neoadjuvant therapy and determined whether imaging change correlates with disease free survival.

We queried a database of 674 ILC cases treated at UCSF from 1981-2017 and identified all patients treated with NAT. We reviewed MRI reports and recorded BIRADS descriptors of findings, maximal tumor diameter for mass or non-mass enhancement (NME), and subjective radiologist comments on progression or improvement. We used the t-test, chi-squared test, Pearson's correlation, and Kaplan Meier survival estimates in Stata 14.2.

We identified 136 patients with ILC treated with NAT and included 101 who had a post-treatment MRI report available. Maximal diameter on post-treatment MRI underestimated pathologic tumor size by a mean of 3.3 cm (range -3.6 to 15.3 cm) for masses and 1.87 cm (range -7.2 to 9.7 cm) for NME. MRI underestimated true size of masses by ≥1 cm in 61.5% of cases; this size discrepancy was associated with increased positive margins (46.4% versus 20%, p=0.011). NME size on MRI underestimated true size by at ≥1 cm in 65.6% of cases. The correlation coefficient between mass size on MRI and true size was 0.34 (p=0.0041), which increased to 0.67 (p<0.0001) when excluding those with associated NME. For NME, the correlation coefficient between size on MRI and true size was 0.28 (p=0.1239). Subjective progression on post-treatment MRI was associated with increased recurrence rates (80% versus 18.3%, p=0.001). Subjective improvement on MRI was associated with a trend towards longer disease free interval (89% versus 73% disease free at 4 years, p=0.13).

Maximal tumor diameter on MRI after NAT in ILC vastly underestimates true tumor size. While these findings suggest caution when using MRI for surgical planning in patients with ILC, particularly in cases with NME, the trend towards improved disease free survival in those with subjective improvement is intriguing and suggests that MRI changes could become an early predictor of outcomes.

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Detection and Biomarkers #11

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

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Abstract
Introduction: Breast cancer biomarkers, including estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2), are critical in determining patient prognosis and treatment. Reagent shortages, lack of trained staff and long processing times limit their utility in Tanzania.

Aim: To compare the GeneXpert® Breast Cancer STRAT4 (Research Use Only) assay, to immunohistochemistry (IHC) on corresponding cell blocks using fine needle aspiration (FNA) specimens.

Methods: All patients with a breast mass presenting to the FNA Clinic at Muhimbili National Hospital (MNH) in Dar es Salaam, Tanzania were invited to participate in the study. Inclusion criteria included patients with a suspected diagnosis of breast cancer based on rapid on-site evaluation (ROSE), females and males greater than 18 years of age. Exclusion criteria included a history of breast cancer and pregnant or lactating women. STRAT4 was performed on air-dried FNA specimens at MUHAS and will be compared with ER, PR, and HER2 IHC results on corresponding cell blocks.

Results: All patients recruited were female, median age of 50 years (range 25-78 years). The majority of breast masses were >2 cm (98%, median 6 cm, range 1-28 cm)). The average biomarker turn-around time for FNA and STRAT4 was 4.4 days (range 1-24 days). The average biomarker turn-around time for surgical specimens with IHC 59.4 days (range 20-116 days).

Conclusions: STRAT4 can be implemented in low resource settings as compared to IHC on surgical specimens. STRAT4 promises to be an accurate and rapid method for analysis of breast cancer biomarkers.

Future directions: Compare with IHC results on concurrently collected cell blocks. Implementation and evaluation of the impact of STRAT4 on clinical 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.

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

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

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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.

Epidemiology and Population Science #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

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Abstract

Body: Background: At the UCSF breast screening clinic, intake surveys are sent to women with upcoming mammogram appointments to obtain their demographic data, comorbidities, and assess breast cancer risk (family history, biopsy history). Many patients complete surveys online before their visit. For those who do not, a staff member is present to assist with survey completion on a tablet in-clinic.

Methods: Data was collected from 10,755 patients from December 2012 to 2018. To assess if different survey modalities capture different demographic groups, we analyzed these submissions, comparing responses completed by patients online before visits and in-clinic with assistance.

Results:On average, 48% of invited patients complete a survey. Of respondents 76% completed surveys before visits and 24% completed surveys in-clinic. Both methods captured electronic data that was summarized and presented to clinicians for clinical decision support. Compared to the in-clinic group, a before group patient was more likely to be white, married, and have at least a college education. The before group included a smaller proportion of patients who were Black/African American, Hispanic/Latina, and 65 years or older. Furthermore, a greater proportion of the before group reported 2 or more comorbidities. The before population reported more often having fair or poor health over the preceding 30 days. While these differences were statistically significant, it is important to put some of these results into perspective: while only 24% of survey responses were collected in-clinic, 59.1% of all Black/African American responses and 33.5% of all Hispanic/Latina responses were represented in this group.

Conclusions/Future Directions: 1) Online surveys are completed more often by traditionally well-represented groups. Offering staff supported electronic surveys in-clinic improves the yield and diversity of patients who complete surveys. 2) We will investigate further issues of health care trust, familiarity, and access to adjust our clinic practices. As more studies move surveys entirely online, we need to identify and address factors that prevent patients from completing surveys before appointments. Alternative survey modalities must be made available in accessible ways and integrated into routine clinical practice.

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Epidemiology and Population Science #3

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

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Abstract
The goal of the WISDOM study is to determine if personalized breast screening, compared to annual screening, is as safe, less morbid, enables prevention, and is preferred by women. The study is registered on ClinicalTrials.gov, NCT02620852.

Women ages 40-74 years with no history of breast cancer or DCIS, and no previous double mastectomy, are eligible to join the study online. Participants can elect randomization or self-select a study arm. For all participants, 5-year risk of developing breast cancer is calculated according to the Breast Cancer Screening Consortium (BCSC) model. For participants in the personalized arm, BCSC score is combined with a Polygenic Risk Score (BCSC-PRS), which is determined by genetic mutations and a panel of single nucleotide polymorphisms (SNPs) known to modify breast cancer risk. Risk stratification determines age to start, stop, and the frequency of screening.

As of February 2019, the WISDOM study is open to all eligible women in California, North Dakota, South Dakota, Minnesota, Iowa, and Chicago. To date, 29,157 eligible women have registered and 19,621 women have consented to participate. We analyzed 3,255 participants who have completed risk assessment in the personalized arm. We are partnering with health insurers and self-insured companies using coverage with evidence progression. Enrollment will continue through 2020, and to strengthen generalizability, we are expanding to other states.

To evaluate the addition of PRS, we used paired statistical tests (McNemar) to compare the distributions of BCSC, and BCSC-PRS risk estimates around low-risk (<1.3%), and very-high risk (>6%) thresholds, the latter corresponding to 5-year risk of a BRCA mutation carrier. The median 5-year risk was 1.5% (IQR 1.0-2.1%) using the BCSC model, and 1.4% (IQR 0.8-2.5%) using the BCSC-PRS model. The BCSC-PRS model classified more women into the low (<1%), and very high (≥6%) risk categories compared to the BCSC model alone ($p < 0.001$).

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Our findings demonstrate that incorporating genetic variants into a validated clinical model is feasible and impacts risk classification compared to a model that does not account for genetic risk factors. 5-year results will reveal if this classification improves healthcare value by reducing screening volumes and costs without jeopardizing outcomes.

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Epidemiology and Population Science #4

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

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Abstract
Public health genomics is a rapidly expanding field tasked with the translation of genomic research into population benefits. While the implications for disease prevention are promising, this new era of population-based genomic testing raises many ELSI issues. Our ethnographic study of the WISDOM trial, a novel RCT comparing annual mammography to risk-stratified breast cancer screening based on genetic and traditional risk factors, seeks to elucidate key ethical and social questions raised by genomic screening of a healthy population of women. By using an online consent process without traditional pre-test counseling, the WISDOM trial models how population-based screening would likely be implemented at scale. Women categorized at high or moderate breast cancer risk, including those with a gene mutation, receive a "Breast Health Specialist" (BHS) consultation by telephone involving results disclosure and recommendations for follow up care outside of the study. For this presentation, we present several emerging themes from our analysis of audio recorded BHS consultations and qualitative interviews with women. Our preliminary results suggest that women's preparedness to receive their genetic test results varies widely and is shaped by personal perceptions of risk often tied to family history of breast cancer. Consequently, some women experience ambivalence about undergoing genetic testing, illustrating the disconnect between expectations for personalized screening and the reality of receiving genetic results in a population setting. Furthermore, the structure of this pragmatic trial, and population screening itself, raises questions about how an overburdened health care system will integrate public health genomics into practice and how existing health disparities will be addressed.

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Epidemiology and Population Science #5

Tobacco Exposure and Breast Cancer in the Athena Breast Health Network

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Abstract
Background: Smoking is a known risk factor for various types of cancer, and breast cancer patients who smoke are known to have higher breast cancer mortality. However, few studies have found an association between smoking and breast cancer incidence or tumor biology. The Athena Breast Health Network distributes an intake questionnaire at the UCSF and UCSD breast care centers which can be used to investigate links between tobacco exposure and the characteristics of incident breast cancer.

Methods: Intake questionnaires were distributed to all new patients at the UCSF and UCSD breast care centers from December 2012 to May 2018. Patients who completed the questionnaire with a known diagnosis of breast cancer were compared to those without in a case-control study. Breast cancer diagnoses were determined by ICD9 diagnosis codes from the patients' medical records. The association of smoking and breast cancer prevalence and biology was analyzed using generalized linear models and Fisher tests in R.

Results: Of the 7727 patients who completed the Athena intake questionnaire at UCSF and UCSD, 5499 consented to have their data used for research. A first analysis was conducted on 4175 UCSF patients alone: 2186 of the UCSF patients who had completed the questionnaire had a self-endorsed breast cancer diagnosis, vs 1989 with no known diagnosis at the time of this analysis. 1096/4175 of the UCSF patients reported having ever smoked, including 73 who had accrued 30 or more pack years. Complete pathology data was available for 1120 cancer patients. Controlling for age, more patients with invasive breast cancer reported having ever smoked, with an odd's ratio (OR) of 2.32 (p = .0043). By including DCIS, the OR drops slightly to 2.26 (p = .0058). Taking alcohol consumption into account as a confounder lowered the OR to 2.19 (p = .0454). Overall, the risk of breast cancer increases with each additional pack year (OR = 1.08, p = .0211), independent of age. There are no significant differences in tumor biology for any smoking group.

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Epidemiology and Population Science #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

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Abstract
Background: The National Comprehensive Cancer Network and other agencies recommend that women with a Gail five-year risk > 1.67% of developing breast cancer should be offered risk-reducing counseling and medications. Polygenic risk score (PRS), calculated by adding the individual breast cancer risk association for each common genetic variant (SNP), has been shown to improve risk prediction when incorporated into risk models. We aim to quantify the likely impact on identifying women recommended for risk-reducing strategies by incorporating PRS into the Gail risk model, and to analyze associations between SNP risk alleles and known breast cancer risk factors.

Methods: Our research cohort included 1500 women at elevated risk (Gail risk > 1.67%) and 1500 age-matched women at average risk (Gail <1.67%) from the Athena Breast Health Network, a collaboration between University of California medical centers and Sanford Health. A panel of breast cancer risk SNPs were evaluated from saliva and blood samples (Akesogen Inc; COGS oncochip array). The PRS for each patient was calculated and incorporated into the Gail risk score using a Bayesian framework. Associations between variables were assessed using t-test or ANOVA.

Results: By ANOVA, there is a statistically significant association between the number of breast cancer risk alleles and ethnicity ($p<2E-16$). Applying Tukey post-hoc analysis, we find that Black, Asian and Hispanic women have significantly more risk alleles than do White women. Black women also have significantly more risk alleles than Asian and Hispanic women.

By incorporating PRS into Gail, 21% of average-risk women transitioned from average to elevated risk and thus would be eligible for risk-reducing counseling and therapy. Conversely, the addition of PRS indicated that 28% of elevated risk patient would no longer be recommended risk reducing counseling.
5% and 24% of average and elevated-risk patients, respectively, would be reclassified to high risk (5-year risk of > 3.0%) after the inclusion of genotype testing.

Conclusion: The addition of SNP based PRS to Gail model significantly changes clinical care recommendations due to the reclassification of women as average and elevated risk.

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Epidemiology and Population Science #7

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

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Abstract
Pathogenic variation in BRCA1 and BRCA2 can increase a woman's lifetime risk of breast cancer from the population average of 12% to 65% or higher. Additionally, heritable breast cancers are more aggressive, and strike at earlier ages. Genetic testing is now allowing more women to understand and manage their heritable cancer risk, but the effectiveness of genetic testing is limited by our large gaps in genetic knowledge: even in the well-characterized BRCA genes, upwards of 40% of all variants are of uncertain clinical significance. One reason for this problem is the difficulty in sharing genetic data. To address this issue, the Global Alliance for Genomics and Health (GA4GH) launched the BRCA Challenge to develop efficient and effective public data aggregation on two high penetrance genes, and to lay the technical, legal, and cultural foundations necessary for widespread data sharing. BRCA Exchange, the first work product of the BRCA Challenge, is the largest public source of BRCA variation data, and supports variant interpretation through data aggregation, in silico prediction, and text mining. We are adding new features regularly to BRCA Exchange, and plan to soon expand the set of genes.

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Epidemiology and Population Science #8

Advocating for Diversity in the WISDOM Breast Cancer Screening Study

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Abstract
Advocacy support enhances diversity recruitment in the WISDOM Study (Women Informed to Screen Depending on Measures of Risk). Funded by the Patient-Centered Outcomes Research Institute, with advocates having a key role in design and planning, WISDOM is a 100,000 healthy women preference-tolerant, pragmatic study comparing annual to personalized risk-based breast screening. The novelty of WISDOM personalized screening is the integration of previously validated genetics and clinical risk factors into a single risk assessment model that directs the starting age, timing, and frequency of screening. Importantly, the genetic component of risk is calibrated by race/ethnicity (White, Asian, African American, Hispanic), to provide each woman the most tailored risk assessment. The goal of WISDOM is to determine if personalized screening, compared to annual screening, is as safe, less morbid, enables prevention, and is preferred by women. The study is registered on ClinicalTrials.gov, NCT02620852.

As of February 2019, the WISDOM study is open to all eligible women in California, North Dakota, South Dakota, Minnesota, Iowa, New Jersey and Illinois. To date, 29,157 eligible women have registered and 19,621 women have consented to participate in the trial. The median age is 56 years and participants self report 83% White, 2% African-American, 6% Asian, and 9% Hispanic. To date, WISDOM Study data collected does not reflect the diversity of our potential participant population. We are partnering with health insurers and self-insured companies and expanding enrollment to other states as well as extending enrollment beyond 2019. With the engagement of patient advocates, expanding diversity recruitment will help fill gaps in scientific knowledge resulting in personalized breast cancer screening recommendations for all women.

Athena has fostered partnerships with advocates since its inception in 2009 when the Consumer and Community Advisory Committee (CCAC) was instituted. Today, advocates, partnering with study staff are championing efforts to further WISDOM diversity outreach by identifying key community leaders in women's organizations, local non-profits and faith-based organizations; identifying people who conduct community-based research and have established community relations; developing strategies on how to engage diverse communities such as with presentations, events, and in-community discussions; and helping to bridge technology and other access gaps.

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Epidemiology and Population Science #9

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

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Abstract
Genetic testing can help inform optimal therapies for breast cancer. For example, for women who have a pathogenic genetic variant that drastically increases their risk for developing an additional primary breast cancer, it may be appropriate to consider contralateral risk-reducing mastectomy [1]. To make use of this information, patients need access to genetic testing and counseling in a timely manner. Currently, up to one-third of women with breast cancer who undergo genetic testing receive their results after their surgery [2].

To improve timely access to genetic testing for patients with breast cancer at UCSF, we are piloting a Genetic Testing Station (GTS) model. In this model, clinicians request a same-day visit at the GTS for patients with active-diagnosis breast cancer. The patient receives brief education via videos designed by genetic counselors, and provides consent, family history information, and a saliva sample. The GTS is staffed by Genetic Counselor Assistants under the supervision of licensed Genetic Counselors. If desired by the patient, or required by insurance, genetic counseling with a Genetic Counselor may happen before the test is ordered.

When results are available, the patient receives genetic counseling either by home telehealth (video) or an in-clinic visit. The Genetic Counselor incorporates personal and family history with the results of genetic testing to develop a customized plan of cancer screening and prevention for the patient and their family members. Additionally, results can help guide cancer treatment decisions.

We propose that this model reduces barriers to care, reveals inherited etiologies of breast cancer development, increases access to precision treatment, and facilitates discussion of prevention strategies with patients and their family members. We have found that the breast GTS is a feasible method to improve access to timely genetic testing. In the first 10 weeks of operation, we received consult requests for 33 breast cancer patients; for 26 of those patients, genetic testing was initiated immediately or within a few days. We will further present our initial experience with the GTS, including workflows, obstacles to testing, and mutation yield in patients tested, in comparison to a traditional model for genetic counseling.

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Epidemiology and Population Science #10

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

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Abstract
An important gap in knowledge exists of the influence of ubiquitous exposure to environmental endocrine-disrupting chemicals (EDCs) to racial/ethnic disparities in breast cancer as minorities may be more susceptible due to unequal exposure to EDCs. Phthalates are commonly used in a wide array of consumer products. We prospectively examined pre-diagnostic urinary levels of phthalate metabolites in relation to breast cancer risk in a nested case-control study within the Multiethnic Cohort (MEC). We measured 11 phthalates metabolites and phthalic acid from overnight or first morning urine samples for 1033 breast cancer cases (478 Japanese Americans, 274 Whites, 49 African Americans, 77 Latinos, and 155 Native Hawaiians) and 1033 matched controls using a sensitive isotope dilution high-resolution accurate-mass LCMS assay. Average time between urine collection and breast cancer diagnosis was 5.5 years (SD=3.3). Case and controls were 1:1 matched on area (Hawaii/California), birth year (±1 year), race/ethnicity, urine type (overnight/first morning), date of urine collection (±1 year), hours of fasting (8-10, >10 hours), and time of blood draw (±1 hours). Association of total phthalate exposure (sum of all metabolites + phthalic acid), low-molecular weight phthalates (LMW; MBP, MiBP, MEP, MMP), and high-molecular weight phthalates (HMW; MBzP, MEHP, MEHHP, MEOHP, MECPP, MCMHP, MCHP) with breast cancer risk and lifestyle factors were examined using conditional logistic regression and non-linear associations using restricted cubic splines. All models were adjusted for creatinine levels, demographics, and potential confounders (e.g. established breast cancer risk factors). Overall, no significant associations were observed for total, LMW, or HMW phthalates and breast cancer risk in preliminary analyses. In subgroup analyses by race/ethnicity, suggestive positive associations were observed among the African Americans, Latinos and Native Hawaiians combined (mixed) group (Ptrend=0.03), but not among Japanese Americans or whites. Among control women, total phthalate levels were significantly higher in whites compared to Japanese Americans and the mixed racial/ethnic groups. Overall, significant determinants of LMW phthalate levels included education, neighborhood socioeconomic status, parity, and the Alternative Mediterranean Diet quality index. This first prospective investigation with a large number of minority populations suggest potential racial/ethnic differences in the association of EDC exposure and breast cancer risk.

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Epidemiology and Population Science #11

Conceptual Model of Transdisciplinary Science - Advocacy Collaboration for the Physical Sciences and Oncology: A Case Study Focusing on Breast Density, Biomarker Discovery, and Emerging Therapeutics

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Abstract
BACKGROUND: What happens when you mix the foundations of mechanics with advocacy? In a shared quest for exciting scientific frontiers beyond genomics, Bay Area physical scientists, clinical researchers, and advocates work in dynamic symbiotic relationships to integrate concepts drawn from their respective fields. Focusing on the mechanobiology of tumor progression in breast cancer, researchers and advocates are cocreating system change interventions for revamping convergent research processes.

METHODS: As vital catalysts of transdisciplinary innovation, advocates affiliated with the National Cancer Institute (NCI) Physical Sciences and Oncology Network (PSON) applied core principles that synergize with the evolving disciplines of Implementation Science (IS) and the Science of Team Science (STS). Diverse methodologies to describe the intersections of physical sciences, breast density, biomarker discovery, emerging therapeutics and advocacy are presented. Additionally, we introduced a theoretical framework and conceptual puzzle illustrating multimethod science advocacy engagement strategies, a typology of contextual factors influencing collaboration, as well as the antecedents, processes, strategic priorities, and overall potential impacts of collaborative transdisciplinary science advocacy exchanges.

RESULTS: Through proactive participation in four areas: 1) research and programmatic support, 2) education and outreach, 3) policy and strategy, and 4) representation and advisory, advocates, representing patient/consumer perspectives, worked toward a common set of goals with researchers and clinicians in determining how tumor microenvironments regulate cancer initiation and behavior through interactions among cell types (e.g., initiated cells, activated stromal cells, and components of the extracellular matrix). Applying NCI Office of Advocacy Relations (OAR) and NCI PSON Advocacy Working Group goals for strategic innovation, collaborative execution, and ethical codes of conduct, researchers and advocates codeveloped guiding conceptual frameworks based on organizational foundations, systems readiness, leadership commitment to change, and transdisciplinary levers to promote shared governance, bidirectional collaboration, advocacy inclusion, and the prioritization of research addressing questions of importance to patients.

DISCUSSION: Embedding advocate patient/consumer evidentiary and experiential insights/perspectives regarding mechanics directed research priorities and clinical interventions in the early phase of convergent research efforts contributes to our understanding of the important role of the physical organization in cell-to-cell contacts, tissue architecture, tumor microenviroments, and mechanical properties in response to therapy.

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.

Notably, catalyzing and leveraging advocate engagement across the research continuum provides novel opportunities for advancing institutional changes, spurring unique training/mentoring exchanges, and fostering innovative research and translational opportunities.

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Epidemiology and Population Science #12

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

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Abstract
Introduction: Breast cancer risk reduction has the potential to decrease the incidence of breast cancer. The use of personalized, web-based, risk assessment tools that are directly patient-facing and can be used by genetic counselors can help contextualize the strategies to communicate the chance of developing breast cancer, and potentially increase uptake of chemoprevention.

Methods: A patient-facing, web-based, personalized prevention decision aid prototype was developed to help address the secondary end point of the pragmatic, preference-tolerant randomized control trial called the Women Informed to Screen Depending on Measures of risk (WISDOM) Study.

Results: This poster describes the lessons learned in developing the WISDOM Study's prevention decision aid. The risk assessment workflow and decision aid was demonstrated with patient advocates, decision scientists, genetic counselors, and medical providers, and feedback was incorporated into the tool. The tools was evaluated qualitatively for content, design, and accessibility. Successive quantitative evaluations and pilot will be made for the tool's effectiveness with WISDOM Study participants, starting with a sampling of 20 moderate risk, non-mutation carrier participants in the personalized arm of the WISDOM Study.

Conclusion: The tool represents a shift in the prevention paradigm by providing a personalized, online tool that is accessible for participants and provider facilitators alike. Previous breast cancer decision aids integrate a prevention framework, but require a provider facilitator. This tool was developed to broaden the impact of informed, value-driven, patient-generated knowledge acquisition, and can standardize the delivery of risk information by Breast Health Specialists to WISDOM Study participants. Ultimately, the decision aid will be used to test whether more personalized knowledge of risk contributes to an increased uptake in chemoprevention.

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Epidemiology and Population Science #13

Factors and risk thresholds characterize the women who use chemoprevention

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Abstract
Introduction: The Athena Breast Health Network wants to integrate risk assessment with screening in an effort to identify and reach out to high risk women to consider chemoprevention. We report on factors which contribute to uptake of breast cancer chemoprevention.

Methods: We reviewed 25,392 surveys for 15,228 women who were screened at UCSF between 2011 and 2019 as part of the Athena Breast Health registry. All women in the University of California-wide Athena network reported age and breast cancer risk factors. Gail risk as well as percentile of risk by age was calculated for women without history of breast cancer or DCIS. Breast Health Specialists actively reached out to women in the top 10% of risk by age to discuss risk reduction and chemoprevention.

Results: From 2011-2018, 246 women had Gail Risk Scores in the top 10% of risk for their age group. Of this group, 12 women (4.9%) chose to use chemoprevention and had an average risk of 30.39%, corresponding to the top 2.5% of risk by age. The UCSF screening surveys identified a similarly low rate of chemoprevention (3.5%) as was seen in the overall Athena population. Chemoprevention uptake was positively correlated to higher Gail Lifetime risk scores (OR =1.56; $P < 0.01$), increased age (OR = 1.04; $P < 0.01$), elevated 5-year risk as defined by USPSTF (OR = 1.57; $P < 0.01$), and Ashkenazi Jewish ancestry on both sides of their family (OR = 1.40; $P = 0.01$).

Discussion: A majority of women with a high risk of breast cancer who might benefit did not take chemoprevention. Higher lifetime risk contribute to chemoprevention uptake. This suggests that targeting women with a higher percentile of lifetime risk may be more successful at improving chemoprevention uptake. The findings also suggest the importance of personalized counseling to notify and contextualize their breast cancer risk. A personalized, patient-facing breast health prevention decision aid is being implemented to test if women meeting a higher percentile threshold of lifetime risk are more likely to uptake chemoprevention as part of the Women Informed to Screen Depending on Measures of risk (WISDOM) Study.

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Molecular and Cellular Biology #1

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

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Abstract
Aging is the largest risk factor for breast cancer, with 80% of new cases diagnosed in women over 50y. However, the molecular mechanism underlying age-associated cancer susceptibility is still not well understood. While aging-associated phenotypes in a number of tissues have been correlated with transcriptional and epigenetic changes, few studies have looked at epigenetic regulation at the resolution of individual cell populations. We present a detailed analysis of genome-wide DNA methylation changes at lineage-specific resolution to elucidate how the two major epithelial cells of the breast maintain lineage-specific expression, and how dysregulation of epigenetic mechanisms with age may contribute to increased breast cancer susceptibility. The mammary gland is a branching structure with bilayered epithelia consisting of an apical layer of secretory luminal epithelial cells (LEP) surrounded by a basal layer of contractile and tumor suppressive myoepithelial cells (MEP). In published work, we showed that loss of lineage fidelity in breast epithelia is a key feature of aging. This is observed as a decrease in differential expression between LEP and MEP lineages with age. Interestingly, this loss of lineage fidelity can be imposed by old MEP onto young LEP in a cell non-autonomous manner. Based on DNA methylation data from MEP and LEP populations derived from reduction mammoplasties of younger (<30y) and older women (>55y), we further show that this loss of lineage fidelity is recapitulated in genome-wide DNA methylation changes -- specifically at key regulatory features associated with the promoter region, as well as at annotated CTCF binding sites thought to be involved in chromatin remodeling. Strikingly, this loss of lineage fidelity is driven almost exclusively by differential DNA methylation changes in the luminal population with age, with older LEP acquiring more MEP-like DNA methylation patterns at the dysregulated sites. The lineage bias of age-specific DNA methylation changes suggests that epithelial lineages age via different mechanisms correlated with enrichment of dysregulated CpG sites at certain regulatory regions. This lineage bias, along with age-specific changes in breast composition, may underlie the differences in incidence rates of breast cancer subtypes with age and the prevalence of ER+ luminal-subtype breast cancers in women post-menopause.

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Molecular and Cellular Biology #2

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

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Abstract
Structural breakdown in the mammary epithelium is the hallmark of progression from ductal carcinoma in situ (DCIS) to invasive ductal carcinoma (IDC), and represents a major inflection point in the risk for patients. Normal epithelium is comprised of an inner luminal (LEP) compartment, also the site of origin for most breast cancers, that is surrounded by an outer myoepithelial (MEP) layer. Therefore, we propose that translocation of transformed LEP past the MEP layer is a key rate-limiting step preceding invasion, as most breast cancer drivers are already activated in DCIS lesions. We previously demonstrated that normal human LEP and MEP can self-organize in vitro, and that the capacity of MEP to exclude LEP from the basal compartment is determined by hard-wired and lineage-specific interfacial tensions at each cell-cell and cell-extracellular matrix (ECM) interface. Specifically, the LEP-ECM interface is highly unfavorable compared to the MEP-ECM interface. We hypothesized that cancer driver-induced changes to interfacial tensions lowers the energy barrier for the structural change necessary for basal LEP translocation. Significantly, the strongest prediction from our model is that stabilizing the LEP-ECM interface is necessary for this structural transition. To test this, we expressed nine commonly dysregulated drivers in patient-derived LEP, and quantified their self-organization with normal MEP in 3D-culture and LEP-ECM contact angles (a measure of favorability of the LEP-ECM interface). We found that of these drivers, only PIK3CA-H1047R expression in LEP disrupted their self-organization and dramatic increased their LEP-ECM contact angles. Further, transcriptional analysis confirmed the upregulation of gene modules involved in ECM adhesion and remodeling. These findings are consistent with published engineered mouse models where luminal expression of the Pik3ca-H1047R is sufficient for basal LEP translocation and differentiation within 4 weeks of induction. Collectively, these results show that signaling downstream of PIK3CA, a pathway dysregulated in >70% of breast cancers, drives the physical changes necessary for the structural transition that is a prerequisite for invasion. A more mechanistic understanding of the physical and molecular changes driving this transition will benefit the patients currently being over-treated due to lack of good markers for IDC progression.

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Molecular and Cellular Biology #3

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

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Abstract
An unbiased, label-free, mass spectrometry-based discovery proteomics approach was used to compare protein expression in normal and breast tumor tissues. Peptides were isolated from sections of formalin-fixed, paraffin-embedded specimens (23 normal, 32 tumor), an approach to study malignant human tumors directly rather than indirectly via cell lines or xenografts. Based on Gene Ontology analysis of the entire 1406 protein dataset, the dominant biological process, cellular location and molecular function are cell-cell adhesion (107 proteins), extracellular exosomes (823 proteins) and poly(A) RNA binding (295 proteins). Further analysis of a 629-protein subset shows that the proteins over-expressed in tumors are dominated by RNA binding proteins, many of which are known to regulate splicing. Other over-expressed groups are ribosomal proteins, heat shock proteins and DNA repair proteins. When protein expression is examined as a function of tumor grade, the over-expressed proteins fall into two groups: 1.) proteins whose expression increases monotonically from normal tissue through grade 3 tumors, and 2.) proteins with a biphasic profile, with expression peaking in grade 1. The first, smaller, group includes ribosomal proteins and an elongation factor, consistent with the need for protein synthesis in growing tumors. The second, larger, group is heterogeneous with respect to protein function. It is not known what causes the decline in expression of these proteins in grades 2 and 3 compared to grade 1.

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Molecular and Cellular Biology #4

Host irradiation promotes aggressive tumors by affecting anti-tumor immunity

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Abstract
Anti-tumor immunity represents a target for both prevention and targeted therapy in aggressive mammary carcinoma. We used a radiation-genetic mammary chimera to evaluate the effect of radiation on host biology in the development of Trp53 null mammary cancer. Compared to non-irradiated mice, host irradiation elicited more metastatic, faster-growing tumors and shifted the tumor spectrum. Here we investigated the hypothesis that host irradiation modifies anti-tumor immunity, both local and systemic, to shape the diversity of mammary cancers. Using gene expression profiling and Phenoptics® quantitative pathology, we stratified tumors from irradiated versus sham-irradiated mice. Gene expression profiling invoked greater inflammation and decreased immune surveillance signatures in tumors from irradiated hosts. Consistent with this, tumors arising in irradiated animals had elevated cyclooxygenase-2 (COX2) gene expression and protein by immunostaining. Quantitative pathology showed that tumors arising in irradiated hosts were enriched in COX2-associated immunosuppressive myeloid cells. Tumors from irradiated hosts were also characterized by pathways associated with immune suppression as evidenced by decreased expression of cytokines and chemokines necessary for migration and recruitment of immune cells. Quantitative pathology showed that tumors arising in irradiated hosts lacked lymphocytes. Recently, human cancers have been classified by patterns of immune cell infiltrate that are called inflamed, excluded and desert. Strikingly, tumors arising in non-irradiated mice were either inflamed or excluded whereas tumors arising in irradiated hosts were either excluded or deserts; the latter of which were the fastest growing tumors. To test whether immunomodulation was critical, mice were fed caffeic acid phenethyl ester (CAPE) in standard chow. Tumors arising in CAPE-treated irradiated mice lacked tumor immune signatures and the rapid tumor growth rate evident in irradiated controls. These data suggest ionizing radiation exposure has a systemic effect that alters the anti-tumor immunity and establishes a highly significant correlation between inflammatory responses and suppression of anti-tumor immunity associated with aggressive tumors as a consequence of irradiated host biology.

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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

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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.

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Molecular and Cellular Biology #6

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

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Abstract
The transcription factor MYC is a pleiotropic proto-oncogene that dynamically regulates numerous cellular functions during transformation, including metabolism. We and others have shown that MYC is disproportionately upregulated in triple-negative breast cancer (TNBC) as compared to estrogen receptor-, progesterone receptor-, and human epidermal growth factor 2 receptor-positive (RP) breast cancers. MYC is known to regulate metabolism in cancer, but its specific influence on pathways of fatty acid (FA) metabolism is unexplored. We found that mitochondrial fatty acid oxidation (FAO) is upregulated in MYC-overexpressing TNBC (MO-TNBC), and that inhibition of FAO decreases both bioenergetic metabolism and primary tumor growth, indicating that MO-TNBC specifically rely on FAO. Increasing FAO requires greater availability of FA at the mitochondria, necessitating altered FA trafficking. However, the mechanism by which MO-TNBC satisfy this requirement to permit increased FAO is unclear. Here, we describe alterations FA uptake and trafficking machinery observed specifically in MO-TNBC.

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Molecular and Cellular Biology #7

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

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Abstract
BRM and BRG1 are necessary but mutually exclusive subunits of the SWI/SNF ATP-dependent chromatin remodeling complex. We have shown that oncogenic downregulation of BRM promotes malignancy of mammary epithelial cells (MECs) and loss of BRM expression in breast cancer is predictive of poor prognosis. To explore the physiological role of BRM in the normal mammary gland, we studied BRM germline knockout mice (BRM KO) and observed a 40% increase in animal size compared to wild type littermates. Developing BRM KO mammary glands revealed enhanced ductal branching, a 60% increase in numbers of terminal end buds and elevated proliferation of BRM KO MECs. Picrosirius red staining of mammary glands further demonstrated an accumulation of collagen around epithelial ducts in BRM KO mice that correlated with an upregulation of genes encoding the extracellular matrix (ECM) proteins Collagen-I and Fibronectin as well as collagen remodeling enzymes. Subsequent flow cytometry analysis of mammary glands demonstrated a preferential expansion of the basal lineage in BRM KO mice compared to controls. Basal MECs are in direct contact with the ECM and mammary stem cells are proposed to exist within this population. To investigate the possibility that BRM KO augments mammary stemness, we performed colony formation and limiting dilution transplantation assays, which served to confirm that the expanded basal population was indeed associated with elevated MEC stem/progenitor activity. To gain more mechanistic insight, we sorted MEC populations for qPCR analysis and found that BRM KO MECs produce more abundant gene transcripts associated with stemness. Our preliminary data now suggest a compensatory upregulation of BRG1 in BRM KO MECs and elevated expression of several known YAP/TAZ target genes involved in the control of cell proliferation. Finally, to describe a role for BRM in tumor progression, we examined the outcome of BRM KO in MMTV-NEU mice and observed more rapid tumor growth with a trend to higher tumor incidence and metastasis in mice lacking BRM. Taken together, our data indicate that SWI/SNF chromatin remodeling regulates YAP/TAZ control over MEC growth and a loss of BRM expression leads to BRG1-directed ECM remodeling, MEC proliferation and elevated mammary stemness, resulting in heightened mammary 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.

Molecular and Cellular Biology #8

Organoid D2B (Disease to Biology) at Parnassus

Hanna Doh, Alex Samocha, Aseal Birir, Michelle Gbenedio, Philippe Depeille, and Jeroen Roose

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Abstract
Organoids are three dimensional structures generated from primary tissues that retain the ability self-organize into mini-organs, and can be perpetuated indefinitely in culture. Organoids have been instrumental tools to help study biological processes including the stem cell biology of epithelial cell lineages, disease progression, and the role of specific genes or microenvironmental factors in regulating cell behaviors within tissues. Organoids have also been used as clinical tools to screen for biomarkers, to obtain personalized predictive/prognostic information, to test novel therapeutic strategies and rational drug design, and to grow replacement tissues.
In 2018, the Roose lab intiated an Organoid D2B unit at Parnassus. We are generating organoids from mouse models and UCSF patients; including colon, lung, breast, and pancreas. Both organoids from normal tissues as well as tumor organoids from cancer types. We have formalized a collaboration with the HUB4organoids (http://hub4organoids.eu/) and are optimizing standard protocols with the goal of impacting the clinic in the future. The goal for 2019 is to include seven cancer types.

The Organoid D2B team is cryopreserving organoids to generate a centralized, living biobank that will act as a valuable resource to the research community. The Organoid D2B team works on a project basis through collaborations and hopes to provide expertise and infrastructure to UCSF researchers who wish to implement organoid-approaches to their research projects.

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