UNIVERSITY
OF
CALIFORNIA

California Breast Cancer Research Program 2016 Conference:

Joining Forces to Understand the Causes of Breast Cancer

February 29, 2016
South San Francisco Conference Center

CALIFORNIA
BREAST CANCER
RESEARCH PROGRAM

From the Director

Since our inception, the California Breast Cancer Research Program has worked to include and expand the chorus of voices in breast cancer research beyond those normally heard. We have amplified the voices of people directly affected by breast cancer, and we have welcomed the expertise of people in fields complementary to breast cancer research. We have built mechanisms to support community engagement in research. We have expanded the repertoire of breast cancer research by building the portfolios in areas such as the biology of the normal breast, environmental chemicals and breast cancer and breast cancer primary prevention. We've enjoyed tremendous success in including community voices in the structure and direction of our program, application review and project selection, and participation in several research areas. Our model of inclusion has led to improvements in the national and international funding of breast cancer research, but there is still more to be done—more barriers to break down, more silos to topple.

We believe that transformational research is accomplished through the participation of diverse stakeholders in envisioning and executing collaborative research projects. This conference is our newest tool to expand the chorus of voices in breast cancer research. You will enter the conference as an individual. We hope you will leave the conference as part of a chorus—or as duets, trios, and quartets—committed to join in new extraordinary research ventures.

The best breast cancer outcome—our ultimate goal—is to prevent the disease. We believe that breast cancer prevention will require the harmonic effort of researchers, advocates, health care providers, policy makers, research funders, and breast cancer survivors. We all have voices to offer.

Welcome!

Mel Ravenaugh-Lynch

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Program Schedule

7:30am-8:00am — **Location: Lobby**

Breakfast

7:30am-10:00am — **Location: Lobby**

Registration/Check-In

8:00am – 8:15am — **Location: Salon E**

Welcome

Conference Host:

Marjorie Kagawa-Singer
Vice-Chair
California Breast Cancer Research Council

Speakers:

Marion Kavanaugh-Lynch
Director
California Breast Cancer Research Program

Sharima Rasanayagam
Chair
California Breast Cancer Research Council

8:15am – 9:00am — **Location: Salon E**

New Model of Breast Cancer Causation
http://www.cabreastcancer.org/causes/index.php#

Speaker:

Robert A. Hiatt
UC San Francisco

9:00am – 10:30am | **Location: Salon E**

Dissecting Breast Cancer Causation

Moderator:

Joan Venticinque
Breast Science Advocacy Core, UC San Francisco

Speakers:

Psychosocial, Contextual and Biological Contributors to Causation

Sarah Gehlert
Washington University in St. Louis

Breast Cancer Disparities: Factors that Contribute to Causation

Scarlett Lin Gomez
Cancer Prevention Institute of California

Environmental Health – Causal Pathways and Opportunities for Intervention

Lauren Zeise
California Office of Environmental Health Hazard Assessment

10:45am – 12:00pm | **Location: Salon F-J**

Facilitated Conversations

Moderators:

Goal: To access the collective experience and explore our goals, questions and ideas about the future of breast cancer research.

Andrea Dyer
Stacey Smith
Demeter Matrix Alliance

12:00pm – 1:00pm | **Location: Lobby**

Hosted Lunch

1:00pm – 1:50pm | **Location: Salon E**

Resources for Understanding Breast Cancer Causation – Part I

Moderator:

Naz Sykes
National Breast Cancer Coalition

Speakers:

ATHENA: a model for assessing breast cancer risk

Laura Esserman
UC San Francisco

Studying Real-World Breast Cancer Outcomes

Allison Kurian
Stanford University

2:00pm – 3:00pm

Location: Salon E

Resources for Understanding Breast Cancer Causation – Part II

Moderator:

Janice Barlow
Zero Breast Cancer - Retired

Panel Discussion: Conducting Transdisciplinary Research

Speakers:

HERMOSA: Health and Environment Research on Make-up of Salinas Adolescents

Kim Harley
UC Berkeley

Kimberly Parra
Clinica de Salud del Valle de Salinas

Women Firefighters Biomonitoring Collaborative

Heather Buren
United Fire Service Women
San Francisco Fire Department

Rachel Morello Frosch
UC Berkeley

Tony Stefani
San Francisco Fire Department – Retired

3:15 pm – 4:45 pm

Location: Salon F-J

Facilitated Conversations

Moderators:

Goal: to collectively explore what is possible working together and to identify ways we can collaborate to continue to draw upon the knowledge of diverse perspectives.

Andrea Dyer
Stacey Smith
Demeter Matrix Alliance

4:45 pm – 5:15 pm

Location: Salon F-J

Report Back and Closing

Summary of conference outcomes and a discussion of resources for collaboration and next steps following the conference.

5:30 pm – 7:00 pm

Location: Salon E

Reception with Poster Viewing

CBCRP-funded investigators describe their recent findings and new directions.

Advocacy Involvement

Great research starts with you!

Research improves from being directly informed by the experiences and knowledge of people affected: who have or had the disease, who care for people with the disease, or who represent a community impacted by breast cancer.

Advocates

- Do you care about breast cancer research?
- Have you been involved in breast cancer or other community health issues?
- Do you live in California?

If so, please consider registering to be an advocate/community representative for research through the California Breast Cancer Research Program.

Register online: http://tinyurl.com/CABreastCancer-Advocate

Scientists

- Do you have experience working with advocates?
- Have you learned ways to genuinely engage advocates in projects?
- Do you have ideas that you would like to contribute to training efforts that CBCRP develops for scientists?

If so, please come by the California Breast Cancer Research Program booth during breaks and/or lunch to speak with staff and leave your name on our volunteer list for scientists.

CALIFORNIA BREAST CANCER RESEARCH PROGRAM

The California Breast Cancer Research Program (CBCRP) is fighting to end the disease through innovative science and community participation. With a tax check-off contribution, you can join the fight.

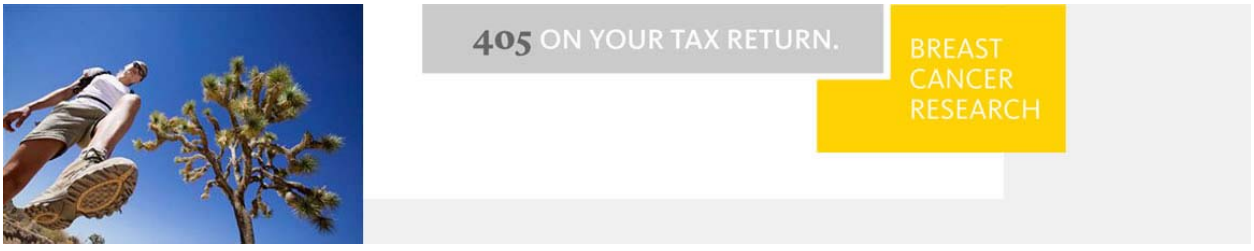
95% of all donations support new approaches to diagnose, treat and prevent breast cancer—approaches other agencies might be reluctant to support. Such as:

- Identifying environmental factors that may cause breast cancer.
- Exploring the potential of natural products in preventing and treating breast cancer.
- Improving support networks to empower breast cancer patients.

The fight's not over.

Check the box. Fund the fight. Mark 405 on your 540 Tax Form. It's an easy, tax-deductible way to help conquer breast cancer.

CHECK 405 ON YOUR STATE TAX FORM TO FUND LIFE-SAVING RESEARCH.



Speaker Biographies (Alphabetical)

Janice Barlow, BSN, NP

Janice Barlow
Zero Breast Cancer - Retired

Moderator: Resources for Understanding Breast Cancer Causation – Part II

After 15 years as executive director, Ms. Barlow recently retired from Zero Breast Cancer. Under her leadership, the organization grew from being grassroots to having a regional and national influence and is a respected model for other communities interested in the prevention and elimination of breast cancer. Beginning in 1995 with a pilot grant from the California Breast Cancer Research Program, Zero Breast Cancer has collaborated with researchers to design research studies that address prevention, the environment, the concerns of women with breast cancer and at risk populations, as well as the importance of community involvement in the research process.

She is especially proud of having played a critical community engagement role in the NIEHS/NCI *Breast Cancer and the Environment Research Program*. Among her many accomplishments is co-authoring two groundbreaking reports, *The California Breast Cancer Mapping Project: Identifying Areas of Concern in California and Breast Cancer and the Environment: Prioritizing Prevention* which fill current gaps in our knowledge and will influence and guide future generations of researchers and public health professionals.

Ms. Barlow continues to be active in the breast cancer community serving on scientific and community advisory boards. Currently, she is member of the UCSF Breast Oncology Program's Breast Scientific Advocacy Core, Athena's Consumer and Community Advisory Committee, and the New Paradigm of Breast Cancer Causation and Prevention Project's Core Team of Experts.

Lieutenant Heather Buren

Heather joined the San Francisco Fire Department (SFFD) in 1997 after running fire crews for a local youth conservation corps. She cross-trained as a firefighter/paramedic in 2002, and was promoted to Lieutenant in 2010. Heather is a co-principal investigator of the Women Firefighters Biomonitoring Collaborative (WFBC) and current president of United Fire Service Women (UFSW).

The UFSW is an employee advocacy group that is committed to being directly involved in recruitment, retention, promotion and education of women in the San Francisco Fire Department.

Heather's interest in health and wellness coupled with her grave concern regarding the staggering breast cancer rates among her firefighter community became the catalyst for a fundraising campaign that raised over $40K and helped fund San Francisco Firefighters Cancer Prevention Foundation and a local breast cancer advocacy group that supports African American women.

Heather Buren
United Fire Service Women
San Francisco Fire Department

Presenter: Resources for Understanding Breast Cancer Causation – Part II

Andrea Dyer

Andrea Dyer is a co-founder of Demeter Matrix Alliance, an alliance of senior practitioners who provide coaching, consulting, education, and facilitation to guide leaders and organizations in their efforts to create sustainable excellence.

Andrea has 30 years of experience as an organization development and change enablement consultant, integral coach, conference and meeting facilitator, workshop leader and educator. She is recognized for integrating practical knowledge of how complex organizations operate with a collaborative approach to create lasting desired results. She is currently focusing her attention on cultivating conversational leadership capability within leaders and organizations to access their collective intelligence, enable innovation and bring about change.

Andrea has a talent for designing and facilitating meetings to work through difficult leadership challenges, initiate new strategic direction, build team and/or organizational capability and cohesiveness, and implement collaborative planning processes within and across organizational boundaries. Clients included not-for-profit, privately held mid-size companies, and large multi-nationals.

Andrea Dyer
Demeter Matrix Alliance

Moderator: Facilitated Conversations

Laura Esserman, M.D., M.B.A.

Laura Esserman, M.D., M.B.A., is a Professor of Surgery and Radiology at the University of California, San Francisco (UCSF) and the Director of the UCSF Carol Franc Buck Breast Care Center. She is a leader of the innovative I-SPY TRIAL model, designed to accelerate the identification and approval of effective new agents for women with high risk breast cancers. The goal of the I-SPY TRIAL model is to shave several years and tens of millions of dollars off the drug development process. The trial paradigm is now being developed for use in other disease domains.

In 2009, Dr. Esserman led the creation of the University of California-wide Athena Breast Health Network, a learning system designed to integrate clinical care and research as it follows 150,000 women from screening through treatment and outcomes. As part of the network, she has spearheaded the development of the WISDOM study to learn how to improve breast cancer screening by testing and comparing the safety and efficacy of a personalized screening strategy informed by each woman's breast cancer risk and preferences against the standard of annual screening.

Dr. Esserman is a passionate and persistent advocate for her patients. She is keenly aware that many of her patients don't have 10 years to wait for the right treatment options. Her work is dedicated to accelerating the development of targeted, effective prevention and treatment options that can make a difference at the time when they are needed the most.

Laura Esserman
UC San Francisco

Presenter: Resources for Understanding Breast Cancer Causation – Part I

Sarah Gehlert, Ph.D.

Sarah Gehlert, Ph.D. is the E. Desmond Lee Professor of Racial and Ethnic Diversity at the George Warren Brown School and Professor in the Department of Surgery at Washington University in St. Louis. She is the Co-Program Leader of the Prevention and Control Program of the Siteman Cancer Center and Co-Director of the National Cancer Institute (NCI)-funded U54 Transdisciplinary Center on Energetics and Cancer (TREC) and serves on the Disparities Elimination Advisory Committee (DEAC) of Siteman's Program for the Elimination of Cancer Disparities (PECaD). Dr. Gehlert was a member of the Executive Committee of Washington University's Institute for Clinical and Translational Science (a CTSA) and chaired it's Center for Community-Engaged Research. She was the Principal Investigator of the P50 Center for Interdisciplinary Health Disparities Research at the

Sarah Gehlert
Washington University in St. Louis

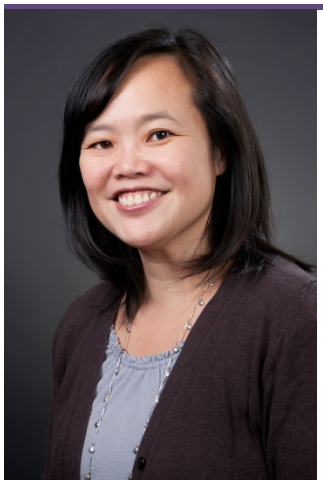
University of Chicago from 2003-2010, where she served as the Helen Ross Endowed Professor, prior to her move to Washington University.

Dr. Gehlert is a Fellow of the Academy of Transdisciplinary Leaning and Advanced Studies and received its inaugural Basarab Nicolescu Award in 2014. She a Fellow of the Academy of Social Work and Social Fellow and serves as Secretary of its Board of Directors and a Fellow of the Society for Social Work and Research. Dr. Gehlert serves on the Council for Extramural Grants at the American Cancer Society and as a Strategy ADvisor of the California Breast Cancer Research Program. She was a member of the Board of Scientific Counselors of the National Human Genome Research Institute at the National Institutes of Health (NIH) from 2010 to 2016. Her publications focus on social influences on health, especially neighborhood and community influences.

Presenter: Dissecting Breast Cancer Causation

Scarlett Lin Gomez, Ph.D., M.P.H.

Scarlett Lin Gomez, M.P.H. and Ph.D. in Epidemiology, is a Research Scientist at the Cancer Prevention Institute of California (CPIC). She is also Co-Investigator of the Greater Bay Area Cancer Registry, a participant in the NCI SEER (Surveillance, Epidemiology, End Results) program and the California Cancer Registry; Consulting Associate Professor in the Department of Health Research and Policy (Epidemiology) at Stanford School of Medicine; and member of the Stanford Comprehensive Cancer Institute. Her research focuses primarily on cancer health disparities and aims to understand the multilevel drivers of those disparities. Dr. Gomez has enhanced the capability of population-level cancer surveillance data to examine the roles of immigration, ethnic enclave, and institutional and neighborhood-level factors. She conducts studies that incorporate mixed-methods approaches to focuses specifically on discrimination, cultural factors, immigration-related issues including stress, and contextual-level influences including family, institutional, and neighborhood factors relating to disparities in cancer incidence and outcomes.



Scarlett Lin Gomez
Cancer Prevention Institute of California

Presenter: Dissecting Breast Cancer Causation

Kim Harley, Ph.D.

Dr. Harley is an Adjunct Associate Professor in the Maternal and Child Health Program and an Associate Director of the Center for Environmental Research in Children's Health (CERCH) at UC Berkeley. She is an epidemiologist whose research examines the impact of common hormone-disrupting chemicals, including pesticides on our food, flame retardants in our furniture, and chemicals found in plastics, on women's reproductive health. Her research interests focus on the role of these common exposures on fertility, timing of puberty, obesity, and pregnancy health.

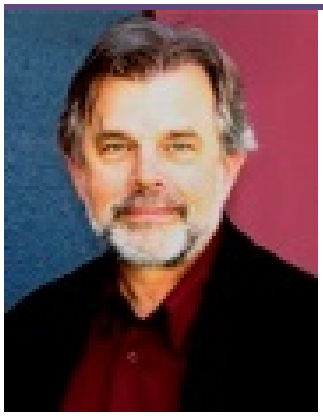
Dr. Harley is the co-director of the HERMOSA Project which is working with Latina adolescents to determine their exposure to hormone-disrupting chemicals in cosmetics and beauty products. She is also the Associate Director of the CHAMACOS Study of immigrant farmworker women and their children living in the Salinas Valley. Her past research has examined the reproductive health of Mexican immigrant women, including the effects of acculturation on diet, social support, and health behaviors, and the effects of occupational exposures, such as pesticides, that disproportionately impact immigrant populations.

Kim Harley
UC Berkeley

Presenter: Resources for Understanding Breast Cancer Causation – Part II

Robert A. Hiatt, M.D., Ph.D.

Robert A. Hiatt, M.D., Ph.D. is Professor and Chair of the Department of Epidemiology and Biostatistics at UCSF, Director of Population Sciences and the Associate Director of the UCSF Helen Diller Family Comprehensive Cancer Center. His research interests include cancer epidemiology, especially breast cancer, cancer prevention and screening, health services and outcomes research, the social determinants of cancer, and environmental exposures in early development related to cancer. He is also an Adjunct Professor, Division of Epidemiology, University of California Berkeley and Adjunct Investigator at the Division of Research, Kaiser Permanente Medical Care Program in Oakland. He was the first Deputy Director of the Division of Cancer Control and Population Sciences at the National Cancer Institute and a past president of the American College of Epidemiology and the American Society for Preventive Oncology. Dr. Hiatt was responsible for the development, approval and management of a new UCSF doctoral program in Epidemiology & Translational Science. He is a member of the National Research Council's Board of Environmental Studies and Toxicology. He received his medical degree from the University of Michigan and his



Robert Hiatt
UC San Francisco

Presenter: New Model of Breast Cancer Causation

doctorate in epidemiology from the University of California, Berkeley.

Marjorie Kagawa-Singer, Ph.D., MA, MN, RN, FAAN

Dr. Kagawa Singer's research focuses on the etiology and elimination of disparities in physical and mental health care outcomes associated with cancer for all communities of color, but primarily with the Asian American and Pacific Islander communities. A major focus of her work is on transforming behavioral science with diverse populations to be inclusive of cultural differences to bring about health equity. This line of research requires testing the cross-cultural validity of health behavior theories and measures, and the implications of these differences for research, clinical care, and community practice. She has also published and lectured nationally and internationally in these areas all along the cancer care continuum from prevention to end of life care.

Dr. Kagawa-Singer is a faculty member of the UCLA Fielding School of Public Health and the Geffen School of Medicine. She is also a member of the Center for Health Policy Research, the Jonsson Comprehensive Cancer Center, and is the Director of Equity, Diversity and Inclusion for the Fielding School of Public Health and a Diversity Officer with Vice Chancellor Jerry Kang's Office of Equity, Diversity and Inclusion for UCLA. She was Chief Editor of the journal, *AAPI NEXUS: Asian American and Pacific Islanders Policy, Practice and Community,* and is a past member of the Board of the National American Cancer Society.

Marjorie Kagawa-Singer
UC Los Angeles

Conference Host

Allison W. Kurian, M.D., M.Sc.

Dr. Kurian is an Associate Professor of Medicine and of Health Research and Policy and Director of the Women's Clinical Cancer Genetics Program at Stanford University School of Medicine. Her research focuses on the identification of women with elevated breast and gynecologic cancer risk, and on the development and evaluation of novel techniques for early cancer detection and risk reduction.

Dr. Kurian has published more than 80 peer-reviewed articles, including several in high-impact journals such as *JAMA*, *Journal of Clinical Oncology*, and *Journal of the National Cancer Institute*. As Director of the Stanford Women's Clinical Cancer Genetics Program, her practice centers on women at high risk of breast and gynecologic cancers.

Allison Kurian
Stanford University

Dr. Kurian serves on several national committees that advance the clinical and research mission of women's cancer genetics: she develops evidence-based practice guidelines as a member of the National Comprehensive Cancer Network, and she recently led the American Society of Clinical Oncology's Scientific Program Committee for Cancer Epidemiology and Prevention.

Presenter: Resources for Understanding Breast Cancer Causation – Part I

Rachel Morello-Frosch, Ph.D., M.P.H.

Rachel Morello-Frosch is Professor in the Department of Environmental Science, Policy and Management and the School of Public Health. Her research examines race and class determinants of environmental health among diverse communities with a focus on social inequality, psychosocial stress and how these factors interact with environmental chemical exposures to produce environmental health inequalities. Much of her work has examined this environmental justice question in the context of ambient air pollution, prenatal exposures to environmental chemicals and effects on developmental outcomes, often using community-based participatory research methods for data collection.

She is also exploring applications of non-targeted approaches to biomonitoring to improve efforts to fully characterize chemical exposures in vulnerable populations, including pregnant women and female occupational groups. As part of this work she is also analyzing the bioethical challenges of exposure assessment and chemical biomonitoring in marginalized communities and how to communicate results in ways that inform study participants about exposure sources and potential health implications.

In collaboration with communities and scientists, she has also worked to develop tools for assessing the cumulative impacts of chemical and non-chemical stressors to improve regulatory decision-making and advance environmental justice goals. Her research is supported by NIEHS, NSF, Cal-EPA, the California Breast Cancer Research Program and private foundations.

Rachel Morello Frosch
UC Berkeley

Presenter: Resources for Understanding Breast Cancer Causation – Part II

Kimberly Parra, B.A.

Ms. Kimberly Parra is Community PI of the HERMOSA Study and the Field Office Manager of the CHAMACOS Study. She has extensive experience working with research participants and managing data collection for community-based participatory research studies,

Kimberly Parra
Clinica de Salud del Valle de Salinas

Presenter: Resources for

particularly with farmworker populations. Ms. Parra was born in the Pajaro Valley, educated at UC Berkeley, and has lived for many years in the Salinas Valley. She is bilingual and bicultural, with strong community roots, having previously worked as a community organizer and youth mentor. She has a particular interest in helping empower youth in her community.

Understanding Breast Cancer Causation – Part II

Captain Tony Stefani

Captain Tony Stefani retired after 28 years of service with the San Francisco Fire Department. In 2006, Captain Stefani founded the San Francisco Firefighters Cancer Prevention Foundation (SFFCPF). The SFFCPF is dedicated to the early detection and prevention of Cancer in both active and retired San Francisco Firefighters. Captain Stefani has also been an advocate supporting legislation on both the State and National level to reduce toxic chemical exposures to firefighters and the population in general.

Captain Stefani received has received numerous awards for his work, including the 2010 San Francisco General Hospital Foundation "Heroes and Hearts" award; the 2010 Phoenix Society of San Francisco Award, in recognition of professional excellence and dedicated service in the San Francisco Fire Department; and the 2012 Greater Geary Boulevard Merchants Association Award 2012, for exemplary dedication to the community outreach and support through the San Francisco Firefighters Cancer Prevention Foundation.

Tony Stefani
San Francisco Fire Department – Retired

Chairman/Founder, San Francisco Firefighter Cancer Prevention Foundation
www.sffcpf.org

Presenter: Resources for Understanding Breast Cancer Causation – Part II

Stacey Smith, B.S.

Stacey Smith brings over 20 years of experience to her roles as a strategy consultant and facilitator, working to build the capacity of organizations to realize their social impact and environmental sustainability goals. During her career she has had the opportunity to build a comprehensive toolbox of approaches to organizational strategy and design, change management, operations excellence and leadership and to apply these in a wide variety of settings in the U.S. and abroad, across the corporate and civil society sectors.

Stacey is an affiliate of the Public Equity Group (PEG) where she leads strategy and organizational design projects for regional and national organizations working on issues across the social equity spectrum. As well, she is a senior policy affiliate of The Keystone Policy Center where she facilitates multi-sector, collaborative

Stacey Smith
Demeter Matrix Alliance

Moderator: Facilitated Conversations

policy making on environmental and resource issues. In her work she has the opportunity to facilitate consensus building across the private, public and civil society sectors through ongoing working groups. She is a facilitator of the national Honey Bee Health Coalition, a group of 38 organizations from the U.S. and Canada working to address honey bee health.

Stacey is a graduate of the University of Vermont with a B.S. in Business Administration. She was a licensed CPA in California in the 1990's and is a founding member of the Society for Organizational Learning on the West coast. She lives in San Francisco with her family.

Naz Sykes, B.S.

Naz Sykes is a proven strategic thinker and leader, and for the past 17 years she has combined "big-picture" strategy with technology and creativity to launch social campaigns and engagement platforms in the non-profit and the entertainment arenas. With a deep passion for the entrepreneurial spirit and all things social**:** social issues, social media**,** and social responsibility**,** she is recognized for her innovative thinking and her expertise in formulating initiatives to engage, empower**,** and mobilize the public.

Through her consulting practice, Naz is currently working with non-profit and for-profit organizations that are creating social initiatives to empower and mobilize the public toward a common goal.

Before her consulting career, Naz has held positions within the non-profit and the for-profit sector. She was the Senior Director for Public Affairs at Lifetime Television and A+E Networks, responsible for high levels of creativity and strategic thinking in order to identify, cultivate, and build successful partnerships. She was responsible for securing exclusive partnerships with Sheryl Sandberg and her Lean In organization, the White House Office of Public Engagement, the White House Correspondents' Association (to name a few) by producing co-branded, one of a kind content, and digital engagement assets to help raise awareness for various social issues. Naz also served as the Executive Director of the Dr. Susan Love Research Foundation (DSLRF). During her eight years at the Foundation, she was the architect of the Love/Avon Army of Women initiative, the first of its kind, online and social initiative, with the goal of recruiting and engaging one million women nationwide to take

Naz Sykes
National Breast Cancer Coalition

Moderator: Resources for Understanding Breast Cancer Causation – Part I

part in breast cancer research studies. Naz also spearheaded the Health of Women Study, the first ever, online breast cancer cohort initiative, studying potential new risk factors for breast cancer and other diseases. Naz also has extensive fundraising experience thanks to leadership positions at UCLA School of Medicine and the UCLA School of Nursing.

Naz currently serves on the Global Breast Cancer Deadline 2020® Campaign Committee, and was the previous chair of the California Breast Cancer Research Program (CBCRP) Council. Naz was selected to participate in the International Women's Forum (IWF) Leadership Foundation 2012-13 fellows program, resulting in leadership and management training at Harvard Business School and INSEAD Business School to the World. Naz received her Bachelor of Science degree in biology and psychology, with a minor in chemistry from the University of Denver.

Joan Venticinque

As a two-time breast cancer survivor, Joan brings her first-hand experience with cancer, augmented by the experiences of others from her community, to provide the patient perspective in cancer research, detection, treatment, prevention and survivorship. In her past work as Manager of Volunteer Resources for Bay Area Cancer Connections in Palo Alto, and with the Cancer Supportive Care Program at the Stanford Cancer Center, she saw first-hand the issues that cancer patients face every day. As a founding member of Bay Area Cancer Connections' Research Advocacy Program, Joan has served as a patient advocate for grant proposals submitted to the California Breast Cancer Research Program, Department of Defense Breast Cancer Research Program, NCI and PCORI. Similarly, she served as a Consumer Reviewer for the Department of Defense Breast Cancer Research Program, LIVESTRONG and PCORI, and is a current member of the Breast Science Advocacy Core, under the Breast Oncology Program at the University of California, San Francisco. Joan also represents patients on the Stanford Scientific Review Committee at the Stanford Cancer Institute, reviewing clinical trials for Stanford patients. She was appointed in September 2015 as a Council Member for the California Breast Cancer Research Program.

Joan Venticinque
Breast Science Advocacy Core, UC San Francisco

Moderator: Dissecting Breast Cancer Causation

Lauren Zeise, Ph.D.

Lauren Zeise, Ph.D., became acting director of OEHHA in May 2015. Dr. Zeise has been with OEHHA since its inception in 1991. She spent 3 years as Deputy Director for Scientific Affairs and 21 years as Chief of the Reproductive and Cancer Hazard Assessment Branch, which included managing the Proposition 65 program. Prior to OEHHA's creation, she was chief of the cancer unit at the California Department of Health Services and spent several years at the California Public Health Foundation and the U.S. Environmental Protection Agency.

She played a leading role in OEHHA's development of CalEnviroScreen, the nation's first comprehensive statewide environmental health screening tool, which is used to identify the California communities most burdened by pollution from multiple sources and most vulnerable to its effects. She also co-led the team that developed the hazard trait regulation for California's Safer Consumer Products program, and she has conducted hundreds of health risk assessments.

Dr. Zeise earned her doctorate from Harvard University with a thesis on "Surrogate Measures of Human Cancer Risk." She has served on numerous national and international science advisory committees and boards focusing on environmental public health and improving the way chemicals are tested or evaluated for health risk. These include more than 20 National Academy of Sciences (NAS) committees, numerous U.S. Environmental Protection Agency panels, and advisory committees for the World Health Organization's International Agency for Research on Cancer. She is a member, fellow, former editor, and former councilor of the Society for Risk Analysis and was the 2008 recipient of the Society's Outstanding Risk Practitioner Award. She is also a member of the Society of Toxicology and an honorary lifetime NAS National Associate.

Lauren Zeise
Acting Director, California Office of Environmental Health Hazard Assessment

Presenter: Dissecting Breast Cancer Causation

UNIVERSITY OF CALIFORNIA

CALIFORNIA BREAST CANCER RESEARCH PROGRAM

QuickStart Training:

Community-based participatory research that addresses breast cancer

California Breast Cancer Research Program, Commonweal and Plumbline Coaching and Consulting invite you to apply to QuickStart, a training opportunity in community based participatory research (CBPR) that addresses breast cancer.

The training will take place this spring and includes two in-person training session, the first in Oakland (week of April 18) and the second in Los Angeles (week of May 23), as well as online training. The training is offered for free for all participants. Travel expenses for participants from California are covered.

Individuals and Teams are Welcome

You are eligible to apply for QuickStart if you are interested in conducting CBPR that includes questions about breast cancer and you are part of an existing or newly formed partnership that includes one academically-trained researcher and one community-member (community-based leader, staff, board member, or volunteer of a community-based organization). Individuals who are interested in CBPR but have not yet found a research partner will be considered if space allows. Priority for participation will be given to teams based in California, though individuals and teams based outside of California who are able to pay their own transportation costs will be considered if space allows.

Applications accepted until training is full. Learn more at cabreastcancer.org/funding-opportunities/crc/quick-start-training.html.
For more information, contact QuickStart@cabreastcancer.org.

Poster Abstracts

Abstract No. 01
Principal Investigator(s): Kimlin Ashing and Florence Britton
Poster Presenter: Mayra Serrano

Evaluating a Clinically and Culturally Informed Survivorship Care Plan Trial for African American Breast Cancer Survivors

Kimlin Tam Ashing[1] (kashing@coh.org), Mayra Serrano[1], Aria M. Campbell[1], Kommah McDowell[2], Shirley Brown[2], Lily L. Lai[3]
Center of Community Alliance for Research and Education (CCARE), City of Hope, Duarte, CA; [1]
Sister Survivor Coalition (CCARE)[2]*; City of Hope National Medical Center, Duarte, CA* [3]

Background: This randomized control study was designed to evaluate the impact of trial participation on access to survivorship care planning (SCP) and adherence to surveillance recommendations among AABCS.

Methods: AABCS were recruited from the State Cancer Registry and support groups. This trial consisted of 1:1 randomization into two conditions: 1) peer navigation + clinically- and culturally-informed breast cancer (BC) materials, and 2) clinically- and culturally-informed BC materials, only. AABCS (*N*= 29) from advocacy groups were trained as peer navigators, with on-going supervision and monitoring by the research team. The ASCO-SCP template was modified based on input from survivor-advocates to increase clinical, cultural, and socio-ecological relevance. The study was implemented using community based-participatory approach. Mailed, self-report assessments were taken at baseline and at 6- and 12-month follow-up.

Results: In total, 112 AABCS who were 6-18 months post initial primary treatment for stage 0-3 BC participated in the study. There was a 74% participation rate and a 64% completion rate. At 6- and 12-month follow-up, 45% and 64% reported access to a SCP, respectively. Improvements from baseline in adherence to SCP surveillance recommendations were observed at 6- and 12- month follow-up assessments regarding physical exam (42.0%, 59.8%, 70.5%, respectively), pelvic exam 36.6%, 47.3%, 44.6%, respectively), breast self-exam (56.1%, 67.3%, 79.6%, respectively), and breast imaging (56.1%, 72.4%, 72.4%, respectively) ($p< 0.05$). There we no significant demographic, medical or study outcome differences by study condition.

Conclusions: Our study findings demonstrate the effectiveness of trial participation in facilitating access to SCP and improved adherence to recommended surveillance. Participation of survivor-advocates in developing culturally-informed BC informational and survivorship care strategies can enhance acceptability and sustainability, especially in community and primary care settings. Untapped opportunities exist for survivor-advocate engagement in survivorship research and practice to address inequities.

Abstract No. 02
Principal Investigator(s): Michael Campbell
Poster Presenter: Breanna Johnson

Breast Cancer and the Human Microbiome

Breanna Johnson, Tess O'Meara, Sarah Theiner, Maribel Campos, Laura Esserman, and Michael Campbell
University of California, San Francisco

The human body contains roughly ten times more bacterial cells than human cells. We now know that there is an interplay between these bacteria and our bodies, in both health and when there is disease present. Inflammatory diseases associated with disruptions in microbial equilibria, such as periodontal disease or ulcerative colitis, as well as chronic antibiotic use, have been associated with increased risk for

cancer development. In a previous small pilot study, we observed differences in the oral microbiomes (the collection of all the different microbes present in the mouth) of women with breast cancer compared to healthy women.

The goal of this research project was to validate our previous findings in a larger cohort of women, as well as extend the microbiomes studied to include the gut and local breast tissue microbiota.

Women with early stage invasive breast cancer or with ductal carcinoma in situ (DCIS) who had not received prior systemic therapy for their disease were eligible for enrollment. A cohort of healthy women was also enrolled. Sample collection kits containing cheek and stool swab materials were distributed to patients in the clinic, and breast tumor tissue was collected from a subset of these women at the time of surgery.

Since many of the bacteria that make up the human microbiome have not been successfully cultured, we used a genomics approach to determine the microbial diversity in these samples. DNA was isolated from these specimens and a portion of a bacterial gene (the 16S rRNA gene) was amplified using the polymerase chain reaction (PCR) and sequenced using high throughput Next Generation sequencing. The 16S rRNA gene is considered the gold standard for studies of microbial communities and for assigning taxonomic names to bacteria.

Oral and gut microbial diversity and richness were assessed at the genus and species levels. Correlations between these markers and clinical variables were evaluated. Finally, various methods (including principle component analyses and classification and regression tree analyses) were employed to identify microbial patterns that could discriminate women with breast cancer vs. DCIS vs. healthy women.

Understanding how microbial diversity relates to breast cancer will open up new opportunities for the development of novel markers for early detection (or markers of susceptibility) as well as new strategies for prevention and/or treatment. For example, perhaps altering the oral or gut microbiomes through better oral hygiene or through the use of probiotics (health promoting “friendly” bacteria often found in yogurt and kefir, for example) would shift a person from having a “cancer microbial profile” to a “healthy microbial profile”, thereby reducing a person’s risk of developing breast cancer or enhancing response to therapy.

Abstract No. 03
Principal Investigator(s): Barbara Cohn

Metabolome-wide Association Study of PCBs in Humans

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Background. Polychlorinated biphenyls (PCBs) are environmental pollutants linked to numerous adverse health outcomes including increased risk of breast cancer. While effects of high-dose PCB exposure have been well characterized, the toxic mechanisms contributing to distal health outcomes from chronic, ambient exposure is not well understood. To provide insight into metabolic perturbations representing a biological response to internal PCB exposure, we performed a metabolome wide association study (MWAS) of environmentally relevant PCB congeners.

Methods. High-resolution metabolomic profiling of plasma obtained from two independent cohorts (397 subjects from California and 74 subjects from Georgia, USA) was completed in tandem with congener specific quantification of PCBs by gas chromatography-mass spectrometry. We combined linear

regression models with *Mummichog*, a software program designed for untargeted metabolomics, to test significant metabolic pathways associated with the plasma PCB levels.

Results. MWAS with PCB congeners 138, 153, 170 and 180 identified significant pathways related to lipid and fatty acid metabolism, including carnitine shuttle, de novo fatty acid biosynthesis, fatty acid activation, glycerophospholipid metabolism and glycosphingolipid metabolism. These results were consistent in both study cohorts, despite their difference in collection period and geological locations.

Conclusions. We report the metabolome wide association of PCBs in humans in two cohorts. Our study provides strong evidence of the interaction of PCBs with specific fatty acid and lipid pathways in human populations. Environmental chemicals may act to enhance breast cancer risk via these pathways. Further investigation of the pathways associated with PCBs and other environmental chemicals and their relationship to breast cancer risk is ongoing.

Abstract No. 04
Principal Investigator(s): Barbara Cohn and Laurie Havas

MyCHDSReport: An Online Portal for Reporting Chemical Exposures to Study Participants

Authors: Julia Brody[1], Laurie Havas[2], Katie Boronow[1], Marj Plumb[3], Ruthann Rudel[1], Herb Susmann[1] and Barbara Cohn[2]
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In 1959–1967, researchers asked women giving birth in Oakland, CA, to enroll in a long-term study of the influence of early life on children's development. Fifty years later, the Child Health and Development Studies (CHDS)—whose participants now include the original mothers, their children, and grandchildren—is a unique study that relates chemical exposures in the womb to breast cancer in multiple generations. Participating families made major contributions to science by donating biological samples for analysis and volunteering their time to answer questions about their health and lifestyle. Some took leadership roles by joining the Participant Advisory Council (PAC). To further engage with cohort members, CHDS researchers and the PAC teamed with Silent Spring Institute to test a web-based tool to report individual results to participants. Researchers interviewed participants about their experiences receiving results.

Previous studies show that participants who have the option to receive individual results feel respected by researchers, choose to review their results, and do not experience excessive worry. Individual report-back enhances environmental health literacy, improves participant retention, and motivates action. Reports that include only the study-wide results replicate important aspects of the individual report-back experience, such as follow-up contact from researchers and increased access to environmental health knowledge. However, participants may be less engaged by study-wide results than by their own findings. We hypothesized that personalized reports will be more effective than study-wide results alone for educating participants and promoting behavior change.

We adapted the digital exposure report-back interface (DERBI) to create an online portal, called MyCHDSReport, to return results to 295 CHDS participants whose blood was tested for 42 environmental contaminants, including banned pesticides, PCBs, flame retardants, and highly fluorinated chemicals. To investigate the effects of reporting personal results, half the women received their personal results highlighted in graphs of study-wide exposure results, and half received only study-wide results at first. All reports included contextual information about the chemicals (including sources of exposure, health effects, and tips for reducing exposure) and key scientific findings from the study. Participants were interviewed before and after receiving their report and responded to an online survey while viewing their report. We collected web analytic data about how participants navigated the report. The digital report and study design were developed in collaboration with the PAC, and a PAC member served as a co-PI of the study.

Participants generally responded positively to the report. Many survey responses expressed appreciation for the information provided. Participants who received individual reports sometimes felt surprised or alarm at the number of chemicals found in their body, but planned to take action to reduce exposure. In contrast, participants who received only study-wide results expressed anxiety over *not* knowing their individual results. Web analytics show that participants who received study-wide results spent less time on average viewing their report. Interview data are still being analyzed. Please visit our poster, which will illustrate the design of MyCHDSReport, present preliminary analytic data, and showcase the experience of a PAC member who is also a co-PI and study participant.

Abstract No. 05
Principal Investigator(s): Christopher Contag
Poster Presenter: Bonnie King

Targeting Breast Cancer Metastasis to Bone

King, Bonnie L., Ph.D[1], Collyar Deborah[2], Contag, Christopher H., Ph.D[1].
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Most breast cancer deaths result from metastasis, a process in which cancer cells depart from the tumor in the breast and travel through the bloodstream to colonize and undermine the function of distant organs. Current treatments for this stage of disease are not curative, and better therapeutic strategies are needed to target breast cancer cells within the metastatic setting. The most common site of breast cancer metastasis is bone. We previously developed a model system for studying breast cancer cell responses within human bone tissue fragments isolated from hip replacement surgeries. The goal of this grant was to adapt our model system for testing therapies to prevent and treat breast cancer metastasis to bone. We predicted that we could measure the response of breast cancer cells to treatment agents as they grow within the bone fragments.

To establish proof-of-principle, we used breast cancer cells that exhibit one of the two common treatment targets: ER (estrogen receptor), which is targeted with Tamoxifen, or Her2 receptor, which is treated with Herceptin. We transferred the breast cancer cells into small bone tissue fragments and monitored cell numbers to show reductions following both treatments. We went on to perform an extended series of experiments in our bone tissue model to study Herceptin responses. We showed that Herceptin specifically and reproducibly reduced the number of Her2+, but not Her2- breast cancer cells growing within bone tissue fragments. Demonstrating the effective modulation of known clinical targets in our human bone tissue model has validated the use of our platform to evaluate new, more effective therapies to prevent and treat breast cancer metastasis to bone.

In the interest of exploring issues relating to the future application of our research on bone metastasis, we also developed a survey to explore breast cancer patient experience and attitudes toward bone marrow exams. Bone marrow exams offer a window into the microenvironment of the bone metastatic niche and constitute a potentially valuable research tool for developing approaches to prevent and treat breast cancer metastasis. The goal of our survey was to explore the potential acceptance of these procedures as a research tool. Our survey was circulated to the METAvivor Foundation email list and was completed by 190 respondents. Preliminary analysis of these results will be presented.

Abstract No. 06
Principal Investigator(s): Andrei Goga

New Approaches to Eradicate Metastatic Breast Cancer

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Despite numerous advances in the advent of chemotherapies and targeted agents over the past decades, metastatic breast cancer remains incurable and essentially a death sentence for afflicted patients. New

discoveries including from The Cancer Genome Atlas (TCGA) and our own research groups at UCSF have uncovered new cancer genes and signaling pathways which are altered in breast cancer, raising the hope that selectively blocking these pathways can allow for the precise eradication of breast cancers. Unfortunately, no single targeted drug to date has proven sufficient to durably eradicate metastatic breast cancers, leading to rapid resistance, recurrence of cancer and ultimately death.

The inability of both conventional chemotherapies and targeted agents to eradicate metastatic cancer is due to several key factors. First, breast cancers are very heterogeneous, made up of billions of cells with various genetic alterations. This heterogeneity means that only some, but not all cells within a tumor, will respond to a particular treatment and die. The subset of cells that do not respond continue to grow, replacing the dying cancer cells with resistant tumor cells. Second, cells within a tumor are constantly evolving to become resistant to new insults. Most normal cells within our bodies have exquisitely precise homeostatic mechanisms that prevent their inappropriate proliferation, invasion or growth at distant sites (i.e. metastasis). Unfortunately, these built-in homeostatic mechanisms have been lost in cancer cells, unleashing their ability to grow and disseminate. Rapid tumor evolution is also facilitated by errors within the tumor cell's ability to sense DNA damage and repair it correctly or to segregate chromosomes precisely during cell replication. Thus, the constant generation of mutations within cancer cells contributes to their rapid evolution towards resistance to new targeted therapeutics.

We hypothesize that breast cancer metastasis can be eradicated, tumor recurrence held at bay, and life extended by simultaneously targeting multiple cancer signaling pathways at once. To achieve this, a new general approach for pre-clinical and clinical development is required which relies on measuring tumor response to new agents as the relevant end-point for a therapy. We postulate that selecting the minimal active dose of a therapy on metastatic tumors should allow us to minimize toxicity from these treatments for patients and most importantly allow us to combine multiple agents to simultaneously target cancer cells. Such approaches we predict will maximize tumor killing and limit tumor evolution and recurrence.

We will present data from the Goga Lab at UCSF regarding the identification and targeting of novel pathways for the inhibition of the most challenging and difficult to treat breast cancers. We seek to translate these promising therapies to clinical trials. Our ultimate goal is to combine these novel targeted therapies for the eradication of metastatic breast cancer.

Abstract No. 07
Principal Investigator(s): Carla Gomez and Meghan Halley

Cancer de Mama: Latinas' Experiences of Breast Cancer Treatment in Santa Cruz County

The goal of this pilot community based participatory research study is to better understand the treatment experiences of low-income Latinas diagnosed with breast cancer, and the factors shaping their decision-making about their breast cancer treatment. Though Latinas are less likely to be diagnosed with breast cancer than White women, when they are diagnosed, they are significantly more likely to die from breast cancer. This is in part because Latinas are less likely to receive regular breast screening. However, there are also differences in the treatments received by Latinas and White women. Though these different patterns of treatment among Latinas with breast cancer are well documented, it remains unclear *why* these patterns exist.

Since September of 2013, our team has been utilizing qualitative and quantitative methods in order to understand key underlying factors – including economic and environmental barriers, socio-cultural norms, and individual goals and preferences – shaping treatment experiences and decision-making among low-income Latinas with breast cancer in Santa Cruz County. Working with our 13 community advisory board members (comprised of advocates, researchers, health care providers, and breast cancer survivors), we completed 25 interviews with Latina breast cancer patients and survivors and their caretakers. In addition, we completed a set of 12 interviews with health care and social service providers serving the Latina community in Santa Cruz County. Though reaching low-income Latinas with breast cancer and their families has been challenging, we have built on our relationships with community partners throughout

Santa Cruz County to ensure our success. Following a rapid data analysis, we presented our preliminary findings in a series of three community forums, two focused on the broader Latino/a community, and one focused on providers serving this population.

We are currently in the final phase of our analysis. Our results document the significant struggles newly diagnosed Latinas face in the period immediately following diagnosis. While many issues arose, two stood out, including: 1) the challenges women faced in understanding and making informed decisions about their breast cancer treatment that were best suited for their values and preferences; and 2) the absence of timely referral to available, essential resources to support them during their treatment. Lack of culturally competent support for women making complex decisions about their breast cancer treatment, as well as delayed connection to essential resources for treatment, led many patients to make decisions that they later regretted. In addition, many also faced serious financial, social and/or emotional burdens as the result of their breast cancer that could have been avoided if they had been provided with timely connection to resources and tailored decision support.

In the next phase of this project, we will draw on the findings from our pilot study to develop, implement and test an intervention to improve breast cancer care for low-income Latinas in Santa Cruz County. If successful, our long-term goal is to disseminate this intervention to improve breast cancer care for low-income Latina populations throughout California and the United States.

Abstract No. 08
Principal Investigator(s): Edward Graves

Effects of Radiation on Tumor Cell Migration and Metastasis

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In our California Breast Cancer Research Program (CBCRP) funded project, we sought to evaluate whether radiotherapy of breast cancers may alter the migration of circulating breast cancer cells. Recently, it has been shown that the process of metastasis, in which tumor cells migrate from their parent tumor to distant sites to form secondary lesions, may function in reverse, resulting in the transit of cells from the circulation and/or secondary tumors back to the primary cancer. We hypothesized that this process of tumor reseeding may limit the efficacy of focal treatments such as radiotherapy, because untreated cells returning to the treated tumor could lead to tumor regrowth. Using *in vitro* migration assays, we observed that irradiation of breast cancer cells results in the production of the cytokine granulocyte macrophage colony stimulating factor (GM-CSF), which increases the migration of tumor cells. Using conformal animal irradiation techniques and bioluminescent imaging of labeled circulating tumor cells (CTCs), we then demonstrated *in vivo* that radiotherapy of orthotopic breast cancers attracts CTCs to the site of irradiation and results in tumor recurrence. Radiation-induced secretion of GM-CSF has been found to be a key driver of this process, and inhibition of this factor can counteract CTC migration and tumor regrowth. Furthermore, we have recently observed that irradiation of normal mammary tissues, muscle, and skin can attract CTCs, suggesting that radiation may similarly attract tumor cells to normal tissues and promote metastasis. These novel findings suggest that cancer radiobiology may be driven not solely by cell kill but also by cell migration, and encourage further investigation of these phenomena in other tumor types and in the clinical setting. We are currently evaluating the significance of these phenomena in human breast cancer patients, and developing therapies to inhibit this process so as to further improve the ability of radiation to cure breast cancer.

Abstract No. 09
Principal Investigator(s): Joanne Hild, Peggy Reynolds and Jane Sellen

Cadmium and Arsenic Exposure in a Mining-Impacted Community: A Community Based Participatory Research Project

Joanne Hild, Executive Director, *Sierra Streams Institute*
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Arsenic (As) and cadmium (Cd), both carcinogenic metals, are pervasive contaminants throughout the Gold Country region of northern California as a result of extensive gold mining that began with the California Gold Rush of 1849. Exposure to Cd has been associated with increased risks of breast and endometrial cancers while inorganic As at low concentrations causes increased growth of estrogen-responsive breast cells. No human health studies had been conducted in this region to determine whether residents have an elevated level of these contaminants in their bodies, despite the fact that the three most populous counties in Gold Country have breast cancer rates that rank in the top ten of the 58 counties in California.

In response to community concerns about elevated breast cancer incidence in the region and the endocrine-disrupting properties of the target metals of interest a study was initiated ("Community Health Impacts from Mining Exposures," CHIME) in collaboration between a community environmental organization, Sierra Streams Institute and a cancer research organization, the Cancer Prevention Institute of California with two specific aims:

Aim 1: Establish a community dialogue about exposure to historical mining contaminants, the purpose and design of a health and exposure study, how best to give back individual study results, and ways to limit exposure, all through community forums and a community advisory board (CAB).

Aim 2. Conduct a pilot biological measurement study to characterize body burden of Cd and As in relation to sociodemographic characteristics, length of residency, residential proximity to mines and mine waste, and the types of daily and recreational activities performed in the Gold Country.

Community input through a CAB directed all phases of the study. A total of 60 women over the age of 21 who were residents of western Nevada County were recruited. Participants completed a questionnaire and provided biological samples consisting of first-morning urine for the measurement of As and Cd. Statistical analyses of the concentrations of these metals and of questionnaire data were conducted to determine the relative contributions of length of residence in Gold Country, activity patterns, and sociodemographic characteristics. Levels for the two metals were compared to those for similarly aged women from the most recent National Health and Nutrition Survey as representative of national averages.

Notable findings from the study were: 1) although on average, cadmium levels in CHIME participants were lower than the national average, they were significantly elevated in women over age 35 who had lived in Gold Country 10 years or more; 2) average levels of arsenic were significantly higher than the national average.

Individual results were returned to participants. Although not a common practice when health effects are not fully understood, the CAB and many community members felt strongly that it was an individual's right to know about her own body levels.

It is hoped that the current research as well as future activities arising from this community-academic partnership will benefit residents of the Gold Country region of California as well as other communities impacted by mining activity.

Abstract No. 11
Principal Investigator(s): Galen Joseph and Alyssa Nickell

Engaging Underserved Women in Health Research

Authors: Alyssa Nickell[1], Janice Cheng[2], Katie Lawlor[1], Susan Stewart[3], Elly Cohen[2,4], Nancy Burke[5], Susan Cohen[2,4], Claudia Guerra[2], Galen Joseph[2]
Affiliations*: [1]Shanti's Margot Murphy Breast Cancer Program; [2]University of California, San Francisco; [3]University of California, Davis; [4]BreastCancerTrials.Org; [5]University of California, Merced*

Background: Underserved breast cancer patients and survivors are typically offered fewer opportunities to participate in cancer research. To address this disparity, Shanti's Margot Murphy Breast Cancer Program (Shanti) initiated a collaboration with UCSF researchers and BreastCancerTrials.org (BCT), a nonprofit clinical trials matching service that led to our successful CBCRP pilot study (2011-2013). The pilot study identified guiding principles for our *Health Research Engagement Intervention (HREI)*: (a) within the context of a trusted relationship, navigators provide education about health research and increase access to information about ongoing breast cancer studies, emphasizing the range of treatment and non-treatment quality-of-life and observational studies; (b) provide education and information at a time when the patient is not in the initial crisis of diagnosis; and (c) address systems barriers to health research information and participation.

Methods: This study uses both qualitative and quantitative research methods to: (1) build capacity for the CBO partner (Shanti) and the health research access point (BCT) and to evaluate the enhancements to both; (2) conduct a prospective randomized controlled trial (RCT) of the HREI with pre and post surveys; and (3) evaluate the implementation of the trial intervention qualitatively. The primary outcome is health research information seeking behavior. Secondary outcomes include health research knowledge, attitudes towards research participation, and health empowerment.

Challenges and Strategies: To address system barriers, we added a multilingual (English, Cantonese, and Spanish) voicemail system to BCT's helpline and enhanced the design of the BCT website for easier navigation by lower health literacy patients. We also implemented a Shanti Client Tracking Calendar to project future enrollment numbers accurately six months out. Our goal is to ensure that these capacity building enhancements are sustainable beyond the grant cycle. Thirty-five of 150 RCT participants have been enrolled to date. To increase the number of eligible participants and speed recruitment, we have expanded the recruitment criteria. We began by enrolling only Shanti clients who are post treatment survivors or metastatic patients with stable disease, and speak English, Cantonese or Spanish. Now, all Shanti clients who speak English, Cantonese or Spanish and have "low care navigation needs" are eligible (i.e. client may or may not still be undergoing treatment but is no longer in the crisis of initial diagnosis or burdened by treatment protocols).

Potential Impact: This study will synergistically improve the capacity of two breast cancer organizations to increase equity in access to health research information and research participation opportunities for diverse underserved breast cancer patients and survivors. The potential impact will be to reduce disparities in access to health research information and participation opportunities, and to produce a dissemination-ready navigator protocol with the potential for replication in underserved communities nationally. Thus, our intervention has the long-range potential to impact progress of breast cancer research.

Abstract No. 12
Principal Investigator(s): Mark LaBarge

Mechanical Stressors and Age as Mediators of Telomerase Regulation

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Background: The ultimate objective of this proposal is to facilitate identification of safe effective interventions that can prevent breast cancer progression from pre-malignant lesions to primary or metastatic cancer. The immediate aim is to explore a novel hypothesis about early stage breast cancer that can radically alter our understanding of the mechanisms underlying carcinoma progression, and may offer specific targets for prevention. Multi-step progression of a normal mammary epithelial cell (HMEC) to breast cancer requires acquisition of errors that permit it to bypass or overcome several distinct tumor-suppressive senescence barriers. Virtually all breast cancers have an error in the RB pathway, have lost vulnerability to oncogene-induced senescence (OIS), and have reactivated sufficient telomerase activity to maintain stable telomere lengths and become immortal. Our research team's studies with the unique, extensive HMEC culture system developed in our labs have shown that errors in the RB pathway are needed to get past a stress-associated senescence barrier, stasis. Errors that reactivate telomerase not only overcome replicative senescence but also eliminate vulnerability to OIS and provide additional malignancy-promoting changes. Consequently, telomerase reactivation is critical for cancer progression.

Hypothesis: We propose that mechano-tensile forces within a cell, which are influenced by the external microenvironment, normally regulate telomerase; exposure to certain types of mechanical stressors will normally inhibit telomerase expression. Further, we hypothesize that early stage breast cancer progression is associated with errors that alter this normal process. When cells bypass stasis (a situation which would be similar to an initial oncogenic hit in normal breast progenitor cells, postulated to be a cancer cell of origin in vivo), the connection between stress and telomerase expression becomes decoupled, and such post-stasis cells are now vulnerable to errors that induce telomerase expression. Cells that overcame stasis require more errors to reactivate telomerase. Our proposal seeks to demonstrate this connection between stressors and telomerase, and uncover the mechanisms responsible for normal regulation and what changes when this connection is lost.

Approach & Results: We are taking advantage of our large bank of normal pre-stasis HMEC from women who ranged in age from 16 to 91 years, and a unique cancer progression series in which the stages of progression from normal finite to immortal malignant have been delineated. We are dissecting the mechanistic basis of mechanical hTERT regulation by culturing cells at different stages in progression on polymer surfaces with tuned elastic modulus, and by identifying key nodes involved in mechano-regulation of hTERT using siRNA, ectopic expression, and pharmacological inhibition of potential signaling nodes. Here we present a description of the HMEC cell system, and the earliest incarnations of these mechano-regulation experiments, which includes the development of a novel quantitative PCR based telomerase activity assay called qTRAP that has enabled preliminary identification of mechano-sensitive pathways involved in telomerase regulation.

Potential for Translation: Because expression of telomerase is essential for malignant progression, interventions that could prevent a decoupling of telomerase regulation by stressors, or restore this connection, could reduce breast cancer incidence, such as by preventing progression from pre-malignant lesions to primary or metastatic cancer.

Abstract No. 13
Principal Investigator(s): Julie Lang
Poster Presenter: Dany Barrak

Molecular Profiling of Circulating Tumor Cells In Non-metastatic Breast Cancer

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Background: Circulating tumor cells are prognostic in all stages of breast cancer (BC), yet few studies have examined their molecular biology in non-metastatic BC. We have previously reported a method for isolation and gene expression profiling of pure CTCs that permits gene expression profiling without background subtraction of leukocytes. We hypothesized that transcriptional profiling of CTCs prior to therapy may predict for pathologic complete response (pCR) to neoadjuvant chemotherapy (NC) in Stage II-III breast cancer.

Methods: We are currently enrolling patients to a prospective, observational clinical study in which CTCs are enumerated and captured from 10-20 mL peripheral blood (PB) via immunomagnetic enrichment based on EpCAM followed by fluorescence-activated cell sorting (IE-FACS). CTCs and tumors are profiled with RNA Seq via the Illumina HiSeq (primary predictor); NanoString PAM50 and real-time polymerase chain reaction will be used as validation studies.

Results: To date, we have isolated CTCs from 29/33 patients (88%). No CTCs were found in 23 healthy controls. The median number of CTCs isolated was 7 (range 0-65). We will analyze our primary endpoint when n=20 and n=40 NC treated patients. Currently 12/33 patients had NC and 21 had no NC; 10/12 patients had CTCs isolated and 5/10 patients had a pCR.

RNA Seq of the first 17 patients CTCs shows clear differentiation between CTCs and PB with 253 differentially expressed genes with a fold-change of at least 2 (false-discovery rate adjusted $p<0.001$). A gene set enrichment analysis of the 17 CTC samples demonstrated up-regulation of cancer related pathways ($p<0.001$). RNA Seq and validation studies of additional CTC and tumor samples is currently in progress

Conclusion: RNA Seq of rare CTCs is feasible in Stage II-III breast cancer and shows evidence of oncogenes and tumor suppressor genes with differential expression.

Abstract No. 14
Principal Investigator(s): Dan Mercola

The HER2 Oncogene Stimulates the Formation of Numerous Super Enhancers which Promote Breast Cancer Metastases

Her2 positive breast cancer (BCa) occurs in 25-30% of cases and is associated with an aggressive phenotype. Multiple HER2-stimulated pathways are known but the list of genes regulated by these events is poorly understood. We previously used RNA polymerase II (POL II) immunoprecipitation (ChIP-chip) together with expression analysis in order to identify gene changes specifically regulated by the HER2 oncogene in cell lines and in breast cancer (BCa) tissues (1). We identified 737 genes that bind POL II in HER2+ breast cancer cell lines but not in HER2- cell lines. Of 737 such genes “poised” for expression only in HER2+ cell lines, 51 were differentially expressed ($p < 0.05$) in HER2+/- BCa cell lines. Of the remaining 686 poised genes 113 were statistically significantly differentially expressed in breast tumors in

a HER2-dependent manner as observed in data for 812 patients. The remaining 573 genes are not differentially expressed in cell lines nor in the 812 examined BCa patients and are termed “stably poised” genes. The 737 genes are listed in ref. (1)

We observed that many of the 113 genes are regulated by “Super Enhancers” (2,3). Super-enhancers are newly recognized DNA structures formed by looping that bring multiple regulatory factors into proximity of target genes and stimulate the production of the target gene proteins. Super enhancers have never been associated with HER2-positive breast cancer before. Moreover, many of the Super Enhancers regulate genes that are steps of crucial cancer pathways. For example six Super Enhancers encode proteins that participate in the formation of tumor cell protrusions that form podosomes and invadopodia – structures that allow tumor cells to migrate and metastasize. Thus this pathway explains one of the most aggressive tendencies of HER2-positvie breast, an enhanced metastatic potential. Inhibitors to several of the steps of the pathway are known which suggest new therapies. We plan to test the utility of these therapies.

In summary, we have uncovered a new mechanism of HER2-positive breast cancer. HER2-positive breast cancer utilizes clusters of Super Enhancers to increase tumor aggression. We propose to test the use of inhibitors to block a key pathway of metastasis.

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Abstract No. 15
Principal Investigator(s): Anna Napoles and Carmen Ortiz

Discovering the Post-treatment Self-care Needs of Spanish-speaking Latinas after Breast Cancer

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Objective: Working with community-based partners, this study sought to identify the most important post-treatment symptom management, psychosocial, and informational needs of Spanish-speaking breast cancer survivors (SSBCS) to inform the development of a peer-delivered intervention to address these needs.

Methods: We conducted a cross-sectional telephone survey of 118 SSBCS, semi-structured focus group and individual interviews with 25 SSBCS, and semi-structured interviews with 5 cancer support providers and 4 breast cancer clinical care providers. We queried all respondents about the symptom management, psychosocial, and informational needs of SSBCS following the end of active treatment.

Results: Mean age of telephone survey respondents was 55 years (SD=12.3), all were foreign-born, most had less than a high school education (66%), most were of Mexican origin (51%), and most had completed active treatment within 2 years (69%). SSBCS who completed semi-structured interviews were similar to telephone survey respondents on demographic characteristics. Surveys identified the five most bothersome (bothered by it in the past month at least “somewhat,” “quite a bit,” or “a lot”) physical symptoms as: joint pain (53%), fatigue (42%), hot flashes (38%), numbness/tingling in hands/feet (35%), and vaginal dryness (30%). The five most bothersome emotional symptoms were thoughts of recurrence or new cancers (42%), depression/sadness (36%), anxieties (34%), stress (32%), and loss of interest in usual activities (24%). Other issues included problems with sleep (40%), memory (33%), and ability to

concentrate (26%). The majority expressed interest in obtaining help with eating a healthier diet (74%), knowing what medical tests are recommended after breast cancer (70%), getting more exercise (69%), managing stress (63%), and doing yoga or meditation (55%). Eight themes emerged from semi-structured interviews: 1) unmet physical symptom management needs; 2) sense of abandonment by health care system post-treatment; 3) need for formal transition from oncology to primary care; 4) social support often ends when treatment ends; 5) challenges resuming roles; 6) elevated anxiety when obtaining follow-up care; 7) desire for information on treatment side effects; and 8) physicians want patients to know about symptom vigilance. SSBCS suggested survivorship programs include emotional support and tools/resources to help with the transition, reintegration back into life (work, social and partner issues), symptoms, and distress.

Conclusions. SSBCS suffer significant post-treatment symptoms and distress and lack information to manage cancer sequelae. This lack of information could interfere with reporting of symptoms to health care providers and adherence to hormonal therapies. SSBCS need culturally appropriate survivorship care programs that address symptom management and psychosocial distress, and provide information on follow-up care, healthy lifestyles, and strategies for coping with role reintegration.

Potential Impact: Results were used to develop a prototype of a peer-delivered survivorship program for SSBCS to be tested in a follow-up study. Obtaining input from survivors and providers should improve the program's relevance and potential usefulness. This program could reduce symptom and psychosocial health disparities experienced by SSBCS and improve the quality of their lives and follow-up care.

Acknowledgements of Funding: This research was supported by funds from the California Breast Cancer Research Program grant number 19AB-2500; grant number 1U54CA153511 from the National Cancer Institute; and grant number 1 P30 AG15272 from the National Institute on Aging.

Abstract No. 16
Principal Investigator(s): Sunita Patel
Poster Presenter: Nicole Delgado

Web-based Assessment of Neurocognitive Outcomes in Long-term Survivors of Breast Cancer from the California Teacher's Study.

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CBCRP Award 19IB-0151 (Patel)

Background: Cancer patients report cognitive difficulties following diagnosis and treatment and are concerned about the potential impact in their daily lives. Treatment-related cognitive effects of breast cancer have been widely studied in recent years. The majority of these have focused on cognition across the two years following treatment, with less attention to outcomes into long-term survivorship. In particular, the role of lifestyle health behaviors and other non-treatment factors following cancer therapies in understanding survivors' cognitive long-term outcomes has yet to be delineated.

A major challenge to conducting research that can address these and other similar questions is the high cost of conducting objective neurocognitive assessments with large groups of participants when administered in the traditional, in-person, interactive manner. We proposed to investigate treatment and non-treatment contributors to cognitive functioning in long-term survivors using an innovative web-based assessment approach. For this report, we investigated cognitive functioning in long-term survivors of breast cancer compared to matched women without cancer from the California Teachers Study (CTS), using both web-based cognitive testing and the traditional, in-person testing procedures. We investigated whether statistically significant differences between breast cancer survivors and their controls on gold-standard traditional tests would also be found on the newer, less-investigated, computerized tests.

Methods: All participants were recruited from the CTS cohort. Women with a confirmed breast cancer diagnosis who were at least five years post treatment, not receiving primary cancer treatment for relapse

or other cancer, and with an active email account on file, were invited for participation via email. Age-matched controls without cancer were recruited at a 2:1 ratio. Along with mailed instructions on paper, a web-based link was emailed to participants for computerized assessment. Telephone assistance was provided as needed. A subgroup of participants who lived within 50 miles of our center was also invited for in-person, traditional neurocogntive assessment.

Results: 214 breast cancer survivors and 122 controls completed web-based testing on their home computer (n=336). Mean age was 68 years averaging 16 years of education. Of these, 63 cases and 57 controls were also seen for in-person traditional testing. Among this subgroup, breast cancer patients had significantly reduced performance on traditional tests of working memory skills compared to controls (p=.02), controlled for age, education, mood and BMI effects. Differences in selected cognitive functioning on web-based computerized tests reached statistical significance for the total sample (p=.05), but not when analyses was restricted to the smaller subgroup sample. Further analyses showed that the patients had faster reaction time but lower accuracy scores on web-based tests compared to controls. Reduced cognitive functioning in survivors was observed only on selected domains rather than across all cognitive functions assessed, and was within the normal range.

Conclusion: Mild differences on selected measures of cognitive functioning were evident in long-term survivors of breast cancer compared to controls without cancer. Of note, results provide preliminary support for the sensitivity of remotely-administered computerized assessment in detecting cognitive differences in adequately powered studies. Web-based cognitive assessment using validated tests holds promise in assessing participants that otherwise could not participate.

Abstract No. 17
Principal Investigator(s): Peggy Reynolds

Association between Serum PBDE Levels and Residential Proximity to Solid Waste Facilities/Landfills or Toxics Release Facilities

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Polybrominated diphenyl ethers (PBDEs), chemicals commonly used as flame retardants, have been the source of some concern for a variety of health outcomes including breast cancer. Some studies have examined the relationship between characteristics of indoor environments and human PBDE body burden, but relatively few have considered the role of outdoor environments as potential exposure sources. We examined the association between serum PBDE levels in California women and residential proximity to solid waste facilities/landfills or toxics release facilities, which may release PBDEs into the environment. 481 participants (median age=66 years; range 40-94 years) from the California Teachers Study provided blood samples in 2011-2013, which were assayed for 19 PBDE congeners via Gas Chromatography/High Resolution Mass Spectrometry DFS. Information on solid waste facilities/landfills was obtained from the California Solid Waste Information System, and for toxics release facilities from the U.S. Environmental Protection Agency Toxics Release Inventory program. Facilities with potential for release of flame-retardants were identified and geocoded, and the distance to each participant's residential address at time of blood draw was computed. Linear regression was used to examine the association between the proximity to those facilities and the serum levels of three most common PBDE congeners (BDE-47, -100 and -153), adjusting for age, race, body mass index and neighborhood (block group) socioeconomic status. Serum PBDE levels were lipid adjusted (ng/g lipid) and log-transformed for analysis. Subjects living within 10km (n=452) from any solid waste facility/landfill had approximately 45% higher serum BDE-47 levels than those living beyond 10km (p=0.04). Dose response was evident for residences within 3-9 km. Similar associations were not observed for BDE-100 or 153, or for proximity to toxics release facilities. Living within 10km of some solid waste facilities/landfills may be related to higher serum BDE-47 levels. More studies are needed to examine potential exposure routes.
Acknowledgements: Funded by CBCRP grant #16ZB-8501.

Abstract No. 18
Principal Investigator(s): Peggy Reynolds
Poster Presenter: Sabrina Crispo-Smith

Comparison of GC-HRMS and GC-MS/MS Methods for the Determination of Persistent Organic Pollutants in Human Serum

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Serum analysis of persistent organic pollutants including polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs), and polybrominated diphenyl ethers (PBDEs), are routinely performed for California Biomonitoring studies, such as the California Teacher's Study. The California Teacher's Study measures levels of persistent organic pollutants in California teachers and administrators serum samples collected from 2011 to present, in an effort to establish links between breast cancer and pollutants. Serum samples are extracted using an automated solid-phase extraction system. The sample extracts required separate injections for PCBs/OCPs and PBDEs on two different columns (a 60m SGE HT8-PCB and a 15m Agilent DB-5ms, respectively) installed on gas chromatograph/high resolution mass spectrometer (GC–HRMS, ThermoFisher, Bremen, Germany). A method for the simultaneous determination of 15 PCBs (-66,-74,-99,-101,-105,-118,-138,-153,-156,-170 -180,-183,-187,-194,-203), 7 OCPs (hexachlorobenzene, b-hexachlorocyclohexane, o,p'-DDT, p,p'-DDT, p,p'-DDE, oxychlordane, and trans-nonachlor), and 5 PBDEs (-47,-99,-100,-153,-154) was developed using gas chromatography/triple-quadrupole tandem mass spectrometry (GC-MS/MS, Agilent, Santa Clara, CA) equipped with a 30m DB-5ms column (Agilent). The method was confirmed using samples from the Arctic Monitoring and Assessment Program. The ease of use, 24 minute run time, and low cost of maintenance made this new method attractive for the projects requiring high throughput, like California Biomonitoring projects. Serum data (n=47 for PCB/OCP and n=297 for BDE) produced from GC-HRMS and GC-MS/MS analysis were compared to determine feasibility of using the GC-MS/MS method as an alternative for these large studies. Sample concentrations were determined using average response factors for the GC-HRMS method while calibration curve interpolation was used for the GC-MS/MS method. Most compounds of interest showed linear relationships in the results between the GC-HRMS and GC-MS/MS with slopes of 1.0 ± 0.2 and Pearson's r values > 0.9, indicating both methods to be generally comparable. However, BDE-47 by the GC-MS/MS method was underestimated by 25%, particularly at high concentrations. The cause of this discrepancy is under investigation. Meanwhile, the issue with BDE-47 was resolved by calculating concentrations using average response factors for the GC-MS/MS method. Our new method improves our throughput and will provide benefits to large cohort studies in the California Biomonitoring Program.

Disclaimer: The views expressed herein are those of the authors and do not necessarily reflect those of the California Department of Toxic Substances Control.

Abstract No. 19
Principal Investigator(s): John Shepherd
Poster Presenter: Benjamin Hinton

A Measure of Regional Mammographic Masking Based on the CDMAM 3.4 Phantom

Benjamin Hinton[1], Serghei Malkov[1], Jesus Avila[1], Bo Fan[1], Bonnie Joe [1], Karla Kerlikowske[2], Lin Ma[2], Amir Pasha Mahmoudzadeh[1], John Shepherd[1]
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Abstract: Interval cancers are defined as cancers diagnosed between normal screening mammogram intervals. One important category of interval cancers are cancers that were large enough to be detected at the time of screening but were masked by overlapping dense and spatially complex tissue. Masking diminishes detectability of tumors in women with dense breasts by 10-20%, which delays treatment and potentially increases cancer mortality. Further, interval cancers are often larger than screening detected cancers and of a more advanced stage once discovered.

We present a model of regional masking using an algorithm that determines the detectability of simulated lesions virtually inserted into raw mammography images. These lesions are based on the thicknesses and diameters of gold disks in the Contrast Detail Mammography (CDMAM) 3.4 phantom, which is widely used to determine contrast detail characteristics of mammography systems. We hypothesize that this model will produce regional detectability maps which would allow for clinicians to use other methods to clear regions with low mammographic detectability due to masking.

We first developed software to virtually insert these simulated gold disks and produced predictions of whether these gold disks would be detectable. We used training and validation data from a set of CDMAM images to tune our detectability algorithm and to validate these detectability thresholds that were produced. We found that for a given diameter of simulated inserted disk, our virtual detection algorithm predicted minimum detectabilities that were within the standard error of actual detectability measurements from the CDMAM phantom.

We then performed this calculation in 0.07 mm^2 regions for the entire breast in a small selection of women who have had screening mammograms. We examined the Image Quality Factor (IQF), a measure of disk detectability where larger IQF values have more detectability and less masking, in regions of high breast density and low breast density. In regions with low breast density, the mean IQF value was 48.2 with a standard deviation of 4.7. In regions with higher breast density, the mean IQF value was 25.6 with a standard deviation of 4.6. This indicates that the IQF value differentiates between regions of high breast density and low breast density.

This is the first work to produce a regional map of mammographic masking based on the CDMAM phantom. This is valuable because mammographic masking is a key factor that reduces detectability of mammography and contributes to interval cancers. With a regional measure of masking, clinical radiologists could identify areas with low detectability and use other methods, such as ultrasound, to clear those regions with low mammographic detectability. This would help reduce the number of biopsies, the overall cost of breast cancer detection, and the stress and uncertainty associated with detecting breast cancer in dense breasts.

Abstract No. 20
Principal Investigator(s): Axel Schönthal

Intranasal Drug Delivery of a Novel Agent for the Treatment of Breast Cancer that has Spread to the Brain

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Overall Goal of Project: There is no effective therapy for breast cancer that has spread to the brain, and such patients are faced with dismal prognosis. We are developing a novel chemotherapeutic agent with high brain-targeted activity that is well tolerated and can be administered via nasal inhalation. Delivery through the nose is expected to support brain-targeted drug activity, while at the same time minimizing side effects throughout the rest of the body. Our goal is to assemble convincing preclinical data, so that this new type of therapeutic approach will receive authorization from the FDA for testing in clinical trials with breast cancer patients suffering from brain lesions.

Description of Work: The efficient delivery of many drugs into the brain is greatly hampered by the blood-brain barrier (BBB), which functions to protect the brain from bacteria and foreign substances, including many therapeutic drugs. We are seeking to overcome this obstacle by modifying existing pharmaceutical agents with the natural compound perillyl alcohol (POH). Our computer modeling has predicted that permanently linking POH to certain drugs can result in a fusion compound that is then able to much better penetrate the BBB. Independently, clinical studies (performed by others in Brazil) have demonstrated that POH can be delivered via inhalation through the nose, resulting in significant therapeutic effects in patients with primary brain cancer. We have combined these two observations to devise a novel therapeutic approach that involves the drug temozolomide (TMZ).

TMZ has been used for over a decade for patients with brain cancer. However, its therapeutic impact is far from optimal, because it enters the brain only sub-optimally. We have fused POH to TMZ, resulting in a novel chemical entity called TMZ-POH or NEO212. We predicted that NEO212 would be effective against tumors in the brain, based on two major features: (i) it would cross the BBB more effectively than TMZ, and (ii) it could also be delivered via nasal inhalation, which would further increase its access to the brain tumor, altogether delivering a therapeutic one-two punch to the tumor.

With support from the CBCRP, we have investigated our predictions in different mouse tumor models. For instance, with the use of mice carrying breast cancer cells in their brains, we found that NEO212 exerted pronounced therapeutic activity. These NEO212-treated animals lived much longer than others that received no treatment or received TMZ as the treatment. Importantly, NEO212 was also effective against breast cancer cells that were drug-resistant. At the same time, treated animals did not show signs of side effects, indicating that NEO212 treatment was very well tolerated.

Potential Impact: We are working on obtaining FDA approval to test NEO212 in patients with breast cancer where malignancy has entered the brain. If successful, these clinical trials will establish NEO212 as a novel therapy that proves superior to the (low-efficiency) treatments currently used in this patient group. Combined with increased quality of life (due to fewer side effects), therapy with NEO212 is expected to reduce morbidity and mortality of breast cancer patients with advanced disease.

Abstract No. 21
Principal Investigator(s): Martyn Smith
Poster Presenter: Sylvia Sanchez

Association between Hormone Receptor Activity Level, Lifestyle and Demographic Factors in Mexican American Women

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Breast cancer risk in U.S. Latinas, although lower than that of non-Latina White women, increases with U.S. birth, and with younger age at migration. Progress has been made in identifying non-genetic factors strongly related to breast cancer risk, including changes in plasma steroid hormone levels like estradiol and testosterone. However, all factors contributing to the lower breast cancer incidence rates among recent Latina immigrants are not yet known. Additional risk factors likely exist, such as environmental chemicals, acting on estrogenic and androgenic pathways and disrupting hormone receptor signaling. The objective of our study was to test the association between different lifestyle and demographic variables with measures of hormone receptor activity in thirty U.S.-born and sixty foreign-born Mexican women from California who participated as controls in the San Francisco Bay Area Breast Cancer Study (SFBCS). Two breast cancer cell lines were used in receptor-mediated bioassays, to assess total activity profiles against estrogen receptors (ER) and glucocorticoid receptors (GR) in the 90 archived plasma samples, and measures were expressed in relative light units (RLUs). In univariate analyses, we found a strong positive association between ER activity levels and age at blood draw ($p=1x10-12$) as well as with menopausal status (lower receptor activity among postmenopausal women, $p<1x10-16$). Using a multivariate regression model, we tested the association between ER activity and multiple anthropometric, lifestyle and demographic factors. ER activity level decreased with every 10% increase in Indigenous American (IA) ancestry ($p = 0.015$). This finding suggests a difference in the level of circulating estrogen-like compounds between women with low IA ancestry and those with high IA ancestry. In addition, there was a positive association between ER activity and postmenopausal hormone therapy use ($p<0.001$). In the model that included foreign-born individuals, we observed a positive association between ER activity and years of residence in the U.S. ($p = 0.043$). GR activity was positively associated with alcohol intake ($p = 0.008$) and height ($p=0.031$), and negatively associated with breast cancer risk ($p = 0.054$). The associations between IA ancestry, hormone therapy use, alcohol intake and height with measures of hormone receptor activity level among Mexican American women suggest that individual behavior and sociocultural environment might affect breast cancer risk through its influence on the endocrine system. Future research will use cutting edge mass-spectrometry based technology to further identify the specific chemical compounds that contribute to these observed associations and possibly to breast cancer risk. If modifiable, these receptor binding ligands could be targets of cancer prevention programs.

Abstract No. 22
Principal Investigator(s): Irene Su
Poster Presenter: Sally Dominick

Intervening on Reproductive Health in Young Breast Cancer Survivors: Development of the Women's Health Survivorship Care Plan

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Background and goal: The goal of this research project is to develop and test the efficacy of the Women's Health Survivorship Care Plan (SCP), a novel survivorship care tool to meet the reproductive health needs of young breast cancer survivors (YBCS) and their healthcare providers (HCPs). Ten percent of the 2.8 million breast cancer survivors in the U.S. were younger than 45 years old when they were diagnosed with cancer. Most of these YBCS will experience reproductive health late effects (hot flashes, fertility concerns, limited birth control options and sexual health problems). As well, YBCS are at higher risk of having a hereditary cancer syndrome. Taken together, these survivorship issues can have a negative impact on quality of life. To address these issues and improve quality of life, we have developed a web-based educational intervention targeting both YBCS and their HCPs.

Hypothesis: We will test the hypothesis that YBCS who receive the SCP will have improved hot flash symptoms, fertility concerns, birth control practices, and sexual function and an increased uptake of genetic risk assessment compared to YBCS who do not receive the SCP. Healthcare providers who receive the SCP will have improved knowledge and preparedness on managing these reproductive health survivorship issues in YBCS, compared to HCPs who do not receive the SCP.

Methods and approaches: To develop the SCP content for each of the 5 survivorship issues (hot flashes, fertility concerns, birth control, sexual health and cancer genetic risk), our research team conducted systematic literature reviews, reviewed professional society guidelines and incorporated clinical expertise into practical and evidence-based educational information geared towards YBCS and their HCPS. For each issue addressed in the SCP, the following content sections were created: 1) "Survivorship Care Plan" - take-home points and action steps outlining management strategies, 2) "What does evidence show?" - a summary of clinical research studies, 3) "What do clinical guidelines say?" - a summary of professional healthcare society guidelines, and 4) "Resources" - a curated list of helpful online resources. Next, focus groups with a total of 37 YBCS (each group had 4-8 YBCS) and structured interviews with 9 HCPs were conducted to review and gain feedback on the content sections for each issue. Based on the feedback and comments from this qualitative research, the SCP content was revised and formatted into a web-based educational intervention that will be tested in a randomized controlled trial starting March 2016.

Impact on breast cancer: The Women's Health Survivorship Care Plan provides up-to-date, evidence-based information on managing hot flashes, fertility concerns, birth control practices, sexual health and cancer genetic risk geared towards YBCS and their HCPs. The impact of this intervention on YBCS and their HCPs will be the provision of an accessible, web-based SCP tool geared towards improving knowledge and providing management strategies for reproductive health survivorship issues after breast cancer.

Abstract No. 23
Principal Investigator(s): Luika Timmerman

A Novel TNBC Therapeutic Opportunity: Cysteine Addiction

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Background: Between 650,000 and 850,000 patients/ year receive chemotherapy to treat their tumors, including essentially all triple negative breast cancer (TNBC) patients. To date, over 100 different types of chemotherapeutics are now commonly prescribed. These drugs are largely non-specific, thus they affect every cell in the body, not just tumor cells. Predictably this means that they can have severe, even life threatening side effects as normal cells are poisoned along with tumor cells during treatment. Based on extensive research, physicians prescribe these drugs at doses that maximize the damage to tumor cells and minimize the damage to normal cells in the body. This is known as the therapeutic window. However the prevalence of harmful side effects observed clinically indicates that the therapeutic window can be small, and most likely varies a bit between different tissues, patients, and tumors. Despite these drawbacks, many lives have been saved by chemotherapeutic use and these drugs remain the mainstay tools used to combat tumors such as TNBC.

Hypothesis: If tumors such as TNBC could *specifically* be made more sensitive to chemotherapeutics, then doctors could prescribe lower drug doses to kill tumors. These lower doses would produce fewer side effects on normal tissues making therapy easier to tolerate, with fewer long-term deleterious effects. Alternatively, for really tough tumors, *specifically* making the tumors more sensitive to chemotherapeutics would increase the ability of chemotherapy to kill or slow tumor growth, without increasing the effects on normal tissues.

Approach and results: Tumors use a molecule named glutathione to inactivate many types of chemotherapy. They also use a molecule named xCT, which is present on tumor cells such as TNBC, to produce glutathione by importing cystine from the environment. We tested whether chemotherapeutics commonly used to treat TNBC were made more potent by co-treating cells with chemical inhibitors of xCT. In ongoing cell culture studies we find that in fact that chemotherapy such as doxorubicin is made more potent by combination treatment with an xCT inhibitor. We are now working to understand the molecular underpinnings of the drug synergy we find and are testing these results using tumors grafted into animals, to determine whether this is as promising as our cell culture studies suggest. While our work is particularly relevant to triple negative breast cancer, it also illustrates how important a clinically approved xCT inhibitor could be for the treatment of many types of cancer, since xCT is active on many types of solid tumors.

Due to the translational potential of this novel therapeutic opportunity, we engaged early with the advocacy community. We focused on three major imperatives for our advocate: collaboration, the acquisition of scientific competence, and the representation of program priorities. The research advocate meets regularly with study investigators, reviews research activities, and raises broad policy issues and TNBC challenges, including disparities issues. Forging credibility in reframing what is at stake on biomedical matters, the advocate attempts to spark innovation, democratize science, and support smarter interventions that expedite the incredible potential of future investments in bioscience.

Abstract No. 24
Principal Investigator(s): Thea Tlsty

Stratifying DCIS Biopsies for Risk of Future Tumor Formation

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While it is estimated that ~62,000 women were diagnosed with pre-cancers or pre-malignant lesions such as ductal carcinoma in situ (DCIS) in 2014, only ~12% of these women will subsequently develop invasive breast cancer with potential to die of the disease. However, the vast majority of women diagnosed with DCIS undergo the same regimen of full breast removal (mastectomy), partial mastectomy or partial mastectomy followed by radio-, chemo-therapy and/or hormone drugs. Thus, many thousands of women are treated unnecessarily with additional radiation, hormonal therapy, and/or mastectomy in order to prevent the progression of an invasive cancer that will not, in fact, occur. This causes unnecessary suffering and side effects in a majority of otherwise-healthy women and places unnecessary demands on healthcare systems. Additionally, ~10% of DCIS patients do not receive adequate intervention, since they develop tumors even when the DCIS is removed.

Our goal is the development of a rapid, inexpensive prognostic clinical test that will provide individual risk information for all women diagnosed with DCIS. Recently, we successfully found several biomarkers that, when expressed in DCIS, accurately predict formation of aggressive invasive tumors (called basal-like breast cancers) years before they form, as well as markers that identify women who will not develop future breast cancers after a pre-cancer diagnosis. Our general methodology was to use novel biological insights from basic studies of how cancer forms and grows to provide us with clues to identify markers that predict future invasive cancers. After the candidate biomarkers are hypothesized, they are tested in biopsy samples that were collected years ago in women that were diagnosed with DCIS and elected to have a subsequent lumpectomy. Standard practice at that time did not propose radiation or hormonal drugs. These women have been contacted through the years to monitor their health and determine if subsequent breast cancer developed. Since it is known which biopsies came from women who did or did not develop a subsequent invasive breast cancer, we can determine if our candidate markers are useful by testing them on the biopsies and evaluating their ability to accurately identify which women developed breast cancer.

For over five decades clinical investigators have tried to identify markers that would predict which women diagnosed with DCIS would be among the ~12% to develop a future invasive tumor. They looked for markers in the size, shape and pattern of the DCIS with no success. In the more recent molecular era, they have evaluated several molecular markers, again with no success. Our biological approach, using a unique and well-studied tissue culture model system, provided the first clues to this important clinical problem. Validation of these markers will allow us to develop a test that would tell a women diagnosed with DCIS about her risk of future breast cancer. Our analysis of how these human breast cells acquire cancer properties has not only provided insights for the prediction of future tumor formation but also for possible approaches to preventive therapy.

Abstract No. 25
Principal Investigator(s): Brenda Elvine Kreis and Terry Uyeki

Exploring Rural Disparities in Breast Cancer Mortality

Uyeki, Terry; Elvine-Kreis, Brenda
Humboldt State University Sponsored Programs Foundation; Breast and GYN Health Project

The Rural Breast Cancer Survival Study is a community-based participatory research pilot study conducted by the California Center for Rural Policy at Humboldt State University, the Breast and GYN Health Project, and community members. Due to higher breast cancer mortality rates reported for Humboldt County, study questions were:

1. What factors are associated with higher breast cancer mortality in Humboldt County?

2. Do women living in frontier or rural areas of California have higher breast cancer mortality rates compared to urban areas of California? How do these breast cancer mortality rates compare to Humboldt County mortality rates?

Data (1990-2010) was analyzed from the California Cancer Registry using 2000 U.S. Census data to calculate 20-year average age-adjusted incidence and incidence-related mortality rates for female breast cancer in California, Humboldt County, rural regions, and urban regions of the state. This study is the first to examine breast cancer related deaths based on population density. Survival analysis of registry data was conducted to explore factors which might explain disparities in breast cancer survival within Humboldt County and among rural and urban areas of California.

Results suggest that Humboldt County has higher incidence and incidence-related mortality rates of invasive breast cancer than the other regions (rural and urban) in California. Rural regions of California have slightly lower incidence and incidence-related mortality rates of invasive breast cancer than urban regions.

Several variables were related to increased risk of death from breast cancer within 5 years of diagnosis: stage, tumor grade, age and marital status at diagnosis.

- Women diagnosed at late stage showed a higher risk of death than those diagnosed at early stage – almost 6 times higher in Humboldt compared to about 5 times higher in the rest of California.
- Women diagnosed at grade 3 or unknown grade showed a higher risk of death than those diagnosed at grade 1; 2-3 times higher in Humboldt compared to over 4 times higher in the rest of California.
- Women who were unmarried at diagnosis showed a higher risk of death than those who were married – over 2 times higher in Humboldt compared to 1.5 times higher in the rest of California.
- Women who were age 65 or older at diagnosis showed a higher risk of death than those who were under age 45 – almost 3 times higher in Humboldt compared to 2 times higher in the rest of California.

Overall, women in Humboldt County with breast cancer were more likely to die within 5 years compared to women in other areas (rural and urban) of the state. Survival rates for women with breast cancer in other rural areas were more similar to survival rates in urban areas, than in Humboldt County.

Five Community Liaisons are advising the project on how to best share study findings with their communities. Eight community forums will be held throughout Humboldt County to disseminate and discuss findings and future research questions with community members towards the goal of improving survival. Findings will be shared via the study's website and through social media.

Abstract No. 26
Principal Investigator(s): Xiao-kun Zhang

Sulindac-derived compounds for breast cancer therapy

Investigator: Xiao-kun Zhang
Institution: *Sanford Burnham Prebys Medical Discovery Institute*

The objective of our IDEA grant application is to identify Sulindac-derived compounds targeting the truncated retinoid X receptor-α (tRXRα) for breast cancer therapy. tRXRα protein is a proteolytically-cleaved RXRα nuclear receptor that is produced in breast cancer cells but not in normal mammary cells. The oncogenic effect of tRXRα is largely attributed to its activation of the phosphoinositide 3-kinase (PI3K)/AKT survival pathway and its inhibition of the kappa B kinase (IKK)/NF-κB inflammatory pathway, two major pathways that are abnormally activated in breast cancer cells to confer their growth, metastasis and drug resistance. We previously discovered that nonsteroidal anti-inflammatory drug (NSAID) Sulindac and Sulindac-derived compounds (analogs) could bind to tRXRα and inhibit its oncogenic activities, leading to the growth inhibition of breast cancer cells. We proposed two aims to address our objective. Aim 1 is to design, synthesize, and characterize Sulindac analogs that can bind to a novel binding site on tRXRα, and Aim 2 is to assess the efficacy and selectivity of Sulindac-derived tRXRα modulators.

We have designed and synthesized over 40 Sulindac analogs. The analogs were evaluated for their binding to RXRα and induction of breast cancer cell apoptosis. Our evaluation showed that K-80003 and related analogs can effectively inhibit the growth of breast cancer cells. Our mechanistic studies demonstrated that some of these analogs suppressed the PI3K/AKT signaling by inhibiting the interaction of tRXRα with the p85α subunit of PI3K, while others inhibited the IKK/NF-κB signaling by preventing tRXRα from binding to tumor necrosis factor receptor-associated factor 2 (TRAF2). Among the analogs, we found K-80003 unique and effective with the ability to not only prevent tRXRα from interacting with p85α and TRAF2 in breast cancer cells but also inhibit tRXRα from interacting with TRAF6 and activation of NF-κB in macrophages. Thus, K-80003 is an effective inhibitor of tumor inflammatory microenvironment by targeting tRXRα-mediated survival and inflammatory pathways both in breast cancer cells and macrophages. Our X-ray crystallographic studies revealed a unique binding mechanism of K-80003, which resulted in the tetramerization of tRXRα but not RXRα, thus providing a molecular explanation for its effective antagonism effect against tRXRα activities. K-80003 is active in the triple negative MDA-MB-231 breast cancer cells. K-80003 alone or combination with another Sulindac analog K-8008 inhibited the growth of breast cancer cells in nude mice and the growth of mammary tumor in the transgenic MMTV-PyMT mouse model of breast tumor. A GMP-compliant manufacturing process for K-80003 has been established. Safety pharmacological studies that included assessments of cardiovascular, CNS, respiratory and gastrointestinal systems have been performed. Toxicological studies comprising acute single dose and repeat dose experiments have been conducted that comprise pharmacokinetic (PK), toxicokinetic (TK) and histopathological assessments. K-80003 displays very desirable toxicological and pharmacological profiles and it is under evaluation by FDA for clinical trial against cancers.

About the Breast Cancer Research Program

CBCRP is the largest state-funded breast cancer research effort in the nation and is administered by the Research Grants Program Office within the University of California Office of the President. CBCRP is funded through the tobacco tax, voluntary tax contributions on personal California income tax forms and individual donations.

Our mission is to eliminate breast cancer by leading innovation in research, communication, and collaboration in the California scientific and lay communities.

- We fund California investigators to solve questions in basic breast cancer biology, causes and prevention of breast cancer, innovative treatments, and ways to live well following a breast cancer diagnosis.
- We involve advocates and scientists in every aspect of CBCRP decision-making, including program planning and grant application review.
- Since 1994, we've awarded over $262 million in research funds to institutions across California.
- Ninety-five percent of our revenue goes directly to funding research and education efforts.

Breast Cancer Research Advisory Council

To continue to fund innovative research, CBCRP relies on the Breast Cancer Research Council. The council is responsible for tracking the trends and opportunities for progress that arise in the breast cancer community, making funding recommendations, and planning future directions of the CBCRP. The council is made up of representatives of those affected by breast cancer and the institutions that can help find a solution.

2015-2016 Breast Cancer Research Council

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ABC/African American Community

Lori Marx-Rubiner (9/1/15-8/31/18)
Breast Cancer Social Media

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