



I. INTRODUCTION

A. BACKGROUND

The National Breast Cancer Coalition (NBCC) is dedicated to ending breast cancer through the power of grassroots action and advocacy. In 2010, NBCC launched **Breast Cancer Deadline 2020**[®] to focus resources and efforts to the areas that will lead to the knowledge needed to end breast cancer. The research component of **Breast Cancer Deadline 2020**[®] includes the Artemis Project[®], an advocate led mission driven approach of strategic summits, catalytic workshops, research action plans and collaborative efforts among various stakeholders. The Artemis Project[®] focuses on two areas:

- **Primary Prevention:** How do we stop people from getting breast cancer?
- **Prevention of Metastasis:** How do we stop people from dying of breast cancer?

Artemis Project[®] participants design and implement research plans and interact through an infrastructure maintained by NBCC that allows collaborations to thrive and progress rapidly. The first Artemis Project[®], begun in 2011, focused on primary prevention. A five-year, strategic plan for the development of a preventive vaccine has been developed and is being implemented through the Artemis Project[®] for a Preventive Breast Cancer Vaccine. A research plan is in place, initial seed grants have been awarded to identify vaccine target, and begin pre clinical work, and regular meetings occur to assess progress and readjust plans.

NBCC convened the Summit on Prevention of Metastatic Breast Cancer on August 26-28, 2011, in Aspen, CO, as the first step in focusing efforts on understanding how to prevent breast cancer metastasis. A thorough analysis of the underlying mechanisms of dormant tumor cells was identified as a key priority in the understanding and prevention of breast cancer metastasis.

NBCC next brought together 17 scientists and advocates to plan a project around tumor dormancy as a fundamental approach for preventing metastasis on June 10-11, 2013, in Walland, Tennessee. There was consensus among the diverse meeting participants that there is little known about breast cancer tumor dormancy, but that addressing this gap in knowledge should be a priority within the field. Participants agreed that increased knowledge could lead to an understanding of how to prevent metastasis for significant numbers of women.

B. PURPOSE OF FIRST ANNUAL MEETING

NBCC's first annual meeting for the Artemis Project® on Prevention of Metastasis convened 28 advocates and scientists with a diverse array of backgrounds, including tumor immunology, biotechnology, molecular biology, and biophysics. The participants acknowledged that the overall goal of the project is preventing metastasis, and while tumor dormancy may play a part in this, it was also deemed crucial to consider other factors that may play major roles in the metastatic process. The specific goals of the meeting were to develop an action plan for the next 12-18 months in the context of **Breast Cancer Deadline 2020®**, identifying specific steps; who needs to be involved; and the potential cost.

C. ATTENDEES

2014 Annual Meeting Participants

Julio Aguirre-Ghiso, PhD, Director, Head and Neck Cancer Basic Research, Director of Solid Tumor and Metastasis Research, Mount Sinai School of Medicine

Leslie Bernstein, PhD, Professor and Director, Cancer Etiology, Dean for Faculty Affairs, City of Hope Beckman Research Institute

Amy Bonoff, MBA, Advocate

Frank Calzone, PhD, Biotech Consultant

Paul Ewald, PhD, Professor of Biology and Director of the Program on Disease Evolution, University of Louisville

Jayanta Debnath, MD, Associate Professor, UCSF Department of Pathology

Silvia C. Formenti, MD, Professor of Medicine; Chair, Department of Radiation Oncology, New York University Medical Center

Gregory J. Hannon, PhD, Professor, Investigator, Howard Hughes Medical Institute, Cold Spring Harbor Laboratory

Pat Haugen, Advocate

Simon Knott, PhD, Post Doctoral Fellow, Cold Spring Harbor Laboratory

Keith Knutson, PhD, Program Director in Oncology, Vaccine & Gene Therapy Institute of Florida, and Associate Professor, Department of Immunology, College of Medicine, Mayo Clinic

Mark LaBarge, PhD, Staff Scientist, Life Science Division, Lawrence Berkeley National Laboratory

Debbie Laxague, RN, Advocate

Peter P. Lee, MD, Professor and Associate Chair, Department of Cancer Immunotherapeutics and Tumor Immunology, City of Hope

Susan Love, MD, MBA, Chief Visionary Officer, Dr. Susan Love Research Foundation

H. Kim Lyerly, MD, FACS, Professor, Duke University

Stuart Martin, PhD, Associate Professor of Physiology, Greenebaum Cancer Center, University of Maryland School of Medicine

Musa Mayer, MS, MFA, Advocate

Todd Miller, MD, Assistant Professor of Pharmacology and Toxicology, Dartmouth Hitchcock Norris Cotton Cancer Center

William Muller, PhD, Professor in Departments of Biochemistry and Medicine, McGill University at the Goodman Cancer Center

Josef Penninger, PhD, Senior Scientific Director, Institute of Molecular Biotechnology of the Austrian Academy of Sciences, Full Professor of Immunology and Medical Biophysics, University of Toronto, Professor of Genetics, University of Vienna

Michele Rakoff, Advocate

Patricia Renzulli, Manager, Breast Cancer Grants, National Philanthropic Trust

Joy Simha, Advocate

Patricia Steeg, PhD, Senior Investigator and Deputy Chief, Women's Malignancies Branch, CCR, National Cancer Institute, NIH

Fran Visco, JD, President, NBCC

Alana Welm, PhD, Associate Professor, Oncological Sciences, University of Utah, School of Medicine

Sara Whiting, Advocate

Meeting Support Staff

Annette Bar-Cohen, MA, MPH, Executive Director, Center for NBCC Advocacy Training

Giselle Hicks, MPH, Science Analyst

Isabel Hinestrosa, BA, Programs Assistant, NBCC

Kayla Kirsch, MS, President, Leapfrog Consulting

Marva Lewis, The Event Professionals

II. MEETING & DISCUSSION

The meeting began with a review of the June 2013 tumor dormancy meeting followed by presentations on three issues, below, that had been identified as relevant to tumor dormancy, followed by discussion.

- Oncogene mediated signal transduction in transgenic mouse models of human breast cancer
William Muller, PhD
- Aging and breast cancer
Mark LaBarge, PhD
- Cancer metabolism and autophagy: will these be useful targets in tumor dormancy and preventing breast cancer metastasis?
Jayanta Debnath, MD

The participants then engaged in general discussion around the issues of metastasis and tumor dormancy and agreed upon topics for small group work.

The topics identified were:

1. Human Genetics and Lifestyle Factors
2. Niche: Microenvironment and Host
3. Metabolism
4. Immune System Factors

It was decided that the issues of signaling pathways, modeling, and punctuated equilibrium would be incorporated into all subgroup discussions. Concerns about the relevancy and appropriateness of models were raised throughout the meeting. Participants agreed to first focus on the questions to be answered and then identify appropriate models needed to arrive at answers.

A. SMALL GROUP WORK & OUTCOMES

Human Genetics & Other Lifestyle Factors

Paul Ewald, Greg Hannon, Kim Lyerly, Stuart Martin, Musa Mayer, Todd Miller, Alana Welm, Sara Whiting

This group focused the use of existing data sources to analyze host factors that can impact metastatic outcome. Primary focus was placed on the human model, and the identification of knowledge gaps concerning patient and tumor genetics.

The group discussed mining large datasets to assess risk of metastatic recurrence and/or mortality, and to assess tumor-host interactions. A deep genetic analysis of patient outliers categorized by breast cancer subtype could compare those with an early-stage breast cancer who died within two years of diagnosis and those with a late-stage breast cancer who died more than fifteen years after diagnosis to those with an early-stage breast cancer who survived more than fifteen years and those with a late-stage breast cancer who survived more than fifteen years.

Promising existing datasets to mine include:

- California Teachers Study (germline DNA, long-term follow-up, and breast cancer subtypes)
- Nurses' Health Study (germline DNA, long-term follow-up, breast cancer subtypes, tumor samples)
- Pathways Study of Kaiser Permanente Northern California (single-nucleotide variants, patient records, biological materials)
- Paul Spellman's datasets (done germline/mortality, has tumors)
- METABRIC (Caldas; biological materials)

Recommended Next Steps

1. **Top priority:** Literature review—advocates (what has been done, what data exists)
2. Personnel to gather datasets and organize interactions between groups
3. Personnel to analyze Caldas dataset (METABRIC) from the germline standpoint
4. **Pilot study:** identify outliers and gather samples, design control group (1 year)

After the first round of small group discussions, and a high-level report out, the human genetics and other lifestyle factors group members disseminated among the other three groups.

Niche: Microenvironment & Host

Julio Aguirre-Ghiso, Paul Ewald, Greg Hannon, Simon Knott, Mark LaBarge, Peter Lee, Kim Lyerly, Stuart Martin, Musa Mayer, Michele Rakoff, Joy Simha, Patricia Steeg, Alana Welm, Sara Whiting

The group focused discussion on factors that enable niches to maintain or induce dormancy. A niche was defined as an environment that keeps stem or stem-like cells in a dormant state, with a distinction made between an “active” niche (e.g., lung, lymph nodes, primary tumor) and a “dormant” niche (e.g., bone). The group discussed various changes to the niche that might allow tumor outgrowth, such as genetic variation in the context of environment interactions (“gene-by-environment”), effects of aging, immune function, and cancer treatment itself.

The group used the critical path/accelerator framework¹ to develop an action plan. On the discovery side, the accelerator arm would search for clinical evidence of the existence of different niches.

The critical path outlined by the group included randomized Phase II neoadjuvant trials of existing niche modulators to be identified. The primary endpoint would be time to first metastasis with overall survival as one of the secondary endpoints.

Recommended Next Steps

1. Review the literature for informative clinical studies, dormancy in general with models, evidence for different niches, Isaiah Josh Fidler’s work (<6 months; Julio’s recent review)
2. Find/collect human samples with outcome info—multiple subtypes (1 year; cooperative groups, identify key people – national and international)
3. Get trials going (year 2)
4. Mouse work (year 1-2), look for parallels in human samples (years 2+)

¹ The critical path/accelerator framework was defined during the Fourth Annual Meeting of the Artemis Project® for a Preventive Breast Cancer Vaccine. Time-intensive tasks vital to the realization of the project goal were identified so that they could be advanced in parallel to tasks in the accelerator arm, which consist of steps that could be rapidly completed outside of those in the critical path.

Metabolism & Cell Intrinsic Properties

Leslie Bernstein, Frank Calzone, Jayantha Debnath, Pat Haugen, Keith Knutson, Todd Miller

The focus of this group was to determine the role of metabolism on tumor dormancy and recurrence. The group first distinguished the difference between systemic metabolism (physiological processes in the host) and cell-intrinsic metabolism (genetically-dependent metabolic pathways within tumor cells). By utilizing a model of disseminated tumor cells (DTCs) that give rise to recurrent tumors after a period of dormancy, the group hopes to measure the effects of various metabolic stressors on the transition of DTCs to overt metastases. Experimental stressors were divided into two categories: systemic stressors that would affect overall host metabolism, and cell-intrinsic stressors that would affect metabolic pathways within the tumor at the cellular level.

Recommended Next Steps

1. **Month 1:** Identify correct experimental model and testable genes/stressors
2. **Months 1-12:** Perform human genetic studies (gene expression profiles for matching primaries and metastases)
3. **Months 2-13:** Test the effects of intrinsic (genetic) stressors on DTC recurrence
4. **Months 2-18:** Test the effects of systemic (host) stressors on DTC recurrence
5. **Months 2-5:** Optimize DTC metabolomics (contact Trent Northern)
6. **Months 6-20:** Perform a metabolic and marker analysis of the effect of intrinsic/systemic stressors on DTCs and recurrent tumors

Immune System

Amy Bonoff, Silvia Formenti, Debbie Laxague, Susan Love, Josef Penninger, William Muller

The group focused on the role of the immune system in tumor dormancy and clinical metastasis. Due to the heterogeneity of breast cancer, leveraging the immune system is the best option for prevention of metastasis. The group posited that the immune system typically keeps micrometastases in balance and clinically undetectable. Immune monitoring of breast cancer survivors both before and after metastasis could provide insight on how the immune system works to successfully keep metastasis in check, how it fails in this task, and what changes between these two stages.

Recommended Next Steps

Next 0-12 months

1. Unbiased screening in flies and cell-based systems for metastasis modulators to provide novel candidates for human studies and cross-validation
2. Set-up and characterize mouse models for ER+, ErbB2+, and BRCA1-mutant breast cancer

Next 12-24 months

1. Validation of integrated gene sets in mouse models for ER+, ErbB2+, and BRCA1-mutant breast cancer
2. Focus on innate and adaptive immunomodulators for prevention of metastases
3. First “pre-clinical trials” to combine existing therapies with immunomodulation; find and remove the brakes of acquired and innate immunity
4. Test what “existing” treatments do to the immune system