



I. INTRODUCTION

A. BACKGROUND

The National Breast Cancer Coalition (NBCC) was formed in 1992 to end breast cancer through the power of grassroots action and advocacy. Since that time, NBCC has built a strong coalition of advocates and organizations that raise the awareness of the importance of evidence based approaches in the treatment of breast cancer and raise money for cancer research programs. In 2010, NBCC launched the **Breast Cancer Deadline 2020**[®] campaign that is dedicated to providing resources to develop the knowledge that will end breast cancer by 2020. This innovative program includes the **Artemis Project**[®], the research component that involves researchers, advocates, and other key stakeholders who design and implement research plans that focus 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?

In 2013, NBCC brought together 17 scientists and advocates to develop a strategic plan to prevent metastasis. This plan focused on tumor dormancy as a potential mechanism for preventing metastasis. It was widely acknowledged that while other factors may play a role in metastasis, understanding tumor dormancy and the ability to maintain a dormant state could potentially present a viable clinical option that could prevent the development of metastasis in a significant number of women. The first annual meeting of the Artemis Project[®] on Prevention of Metastasis, held in 2014, convened 28 advocates and scientists and laid the groundwork for a 12 – 18 month strategic plan that focused on understanding of how the immune system can be augmented to induce and maintain metastasis in patients with disseminated disease.

The second annual meeting of the Artemis Project on Prevention of Metastasis was convened in March 2015 in Calistoga, California. The meeting included 40 participants with a diverse set of scientific expertise ranging from immunology, biophysics,

genetics, molecular biology, and clinical oncology. The group reviewed progress since the March 2014 annual meeting, and a follow up planning meeting held in Baltimore, MD in September 2014. The goal of this meeting was to discuss progress in the prevention of metastasis project and to outline goals and action items for the next 18 – 24 months. Discussions focused on the role of the tumor microenvironment and the immune system in tumor dormancy and the prevention of metastasis, and on the evaluation of the cancer stem cell system as a model to control disseminated tumor cell activity.

C. 2015 ANNUAL MEETING PARTICIPANTS

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II. MEETINGS AND DISCUSSION

A. BACKGROUND AND UPDATES SINCE THE FIRST ANNUAL ARTEMIS MEETING ON THE PREVENTION OF METASTASIS, 2014

Progress Reports: Update of Preventing Metastasis Project

Alana Welm

In September 2014, a small subset of Artemis members held a focused Tumor Dormancy meeting to develop an action plan to study the tumor microenvironment or tumor niche. During this meeting, it was noted that the cellular composition or the activation of specific signaling pathways within the cells in the microenvironment that support primary tumor cells might be quite different from those in the microenvironment that support dormant disseminated tumor cells (DTC). Gene expression studies, such as genome wide association studies and/or RNA sequencing might provide informative insight into what propels tumor cells to populate a distal site and what stimulates a cell to remain in or lapse from a dormant, nondestructive state.

While no data has been generated or shared to date, many questions emerged:

1. Are there special patient populations that can be evaluated?
2. Are there correlates between tumor dormancy and other cellular processes, such as the development of antibiotic resistance or the quiescence of stem cells that can be exploited in the tumor dissemination environment?
3. Do metastatic tumor cells use similar pathways as wound healing or EMT?

Advocate Research Project: Existence and Availability of Matched Pairs of Breast Cancer Primary and Metastatic Tumor with Latency

Alice Yaker

Discussions during the September meeting emphasized that a comparison of the microenvironment of primary and metastatic tumors might provide key insights into how tumor dormancy is established, maintained, or terminated. These studies would require matched primary and metastatic tumor samples with latency. Several potential sources of matched pair tissues were identified:

1. NCI Resources:
 - a. Specialized Programs of Research Excellence (SPORE) tissue banks
 - b. National Clinical Trials Network (NCTN)
 - c. Cooperative Human Tissue Network (CHTN)
 - d. Specimen Research Locator
 - e. Program for the Assessment of Clinical Cancer Tests (PACCT)
2. Commercial resources:
 - a. Cureline
3. Researcher Based and other Consortia
 - a. AURORA
 - b. Translational Breast Cancer Research Consortium (TBCRC)
 - c. Army of Women
 - d. Christoph Klein and Klaus Pantel

Additional options such as establishing a rapid autopsy program or creating an Artemis Tissue Bank were discussed.

Recommended Next Steps

1. NBCC will need to clarify how the use of these tissues will advance the goal of preventing metastasis.
2. Issues surrounding ownership, use of a biospecimen for research, cost and quality of biospecimens are issues that will need to be evaluated and addressed.

Subtype Specific Breast Cancer Risk: Integrating Big Data into Breast Cancer Detection

Peter Fasching

Several large studies that include collection of biospecimens are underway in Europe. The AURORA study, sponsored by the Brussels-based Breast International Group (BIG), is collecting serum, plasma, and primary and metastatic tumor samples from 1300 patients with metastatic disease. Similarly, the PRAEGNANT Study Network is collecting whole blood, serum, plasma, circulating tumor cells (CTCs), and primary and metastatic tumor samples from 3500 patients receiving treatment. As of 2014, over 500 patients have been enrolled.

The PRAEGNANT Study Network serves as a biorepository hub for the SUCCESS C study that is currently underway in Germany. This study has

analyzed the correlation between the presence of CTCs and likelihood of developing metastatic disease. A genome-wide association study (GWAS) in these patients has provided a correlation between two single nucleotide polymorphisms (SNPs) and disease free survival in breast cancer patients. These data are preliminary, however, and the analysis of tens of thousands of patients will be needed to draw sufficient correlations between the SNP and phenotypic outcome. Data will also need to be validated to be clinically useful.

Recommended Next Steps

1. Analysis of these data at 2 year and 5 year follow-up intervals could be useful to characterize molecular signatures of dormancy.
2. Research update and future efforts from the Working Groups

Niche microenvironment

Julio Aguirre-Ghiso, Jay Debnath, Paul Ewald, Peter Fasching, Simon Knott, Peter Lee, Kim Lyerly, Alex Swarbrick, Alice Yaker

The tumor niche or tumor microenvironment is considered to be important in the regulation and maintenance of dormancy of disseminated tumor cells (DTCs). Maintenance or establishment of a dormant state might be a successful clinical option to prevent metastasis. However, no tools exist yet that identify or measure dormant cells and no markers of quiescent cells have been developed. Fundamental questions about the composition of the microenvironment and tumor dormancy must still be addressed. These include: what defines a niche? How do these niches change over time? What is the impact of therapy on the composition, signaling pathways, and interaction of cells within a niche? What can the blood tell us about niches and tumor dormancy?

It is feasible that there are candidate genes for dormancy. These could be identified and validated through the evaluation of longitudinal samples from patients with and without disseminated disease. This would also provide insight into if and how dormancy is altered in response to therapy.

Recommended Next Steps

Two main avenues of research emerged from the niche and microenvironment group. The first would investigate if treatment with either tamoxifen or aromatase inhibitors (AIs) induces tumor dormancy in ER+ patients. The second would identify gene

expression signatures of DTCs, biopsies, and CTCs to determine how signatures differ and if CTCs or germline alterations contribute to dormancy.

STUDY 1

1. Literature review to: (1) determine the number of women with and without tamoxifen treatment that developed metastasis and (2) determine the time to metastasis.
2. Retrospective study of samples from ER+ patients with or without tamoxifen treatment to determine gene expression profiles of DTCs.

STUDY 2

1. Compare gene expression signatures in primary tumors and dormant DTCs.
2. Investigate if CTCs could be used as a surrogate marker for a dormant state and if signatures in primary tumors can predict if metastasis will occur.
3. Evaluate if other therapies can also induce or maintain dormancy with fewer side effects.

Stem Cell

Amy Bonoff, Pat Haugen, Keith Knutson, Mark Lee, Stuart Martin, Michele Rakoff, Soledad Sosa, Paul Spellman, Doug Wall, Jason Weber, Alana Welm

Cancer stem cells may provide essential clues regarding the maintenance of a dormant state. If DTCs can be manipulated to remain quiescent, methods to detect dormant or active DTCs can be developed.

It has been shown that tumor cells that are not killed by therapeutic intervention have increased cancer stem cell characteristics. This raises the question, are cancer stem cells linked to dormancy? What can we learn from cancer stem cell signaling and the stem cell microenvironment that will help maintain a dormant tumor cell state to prevent the development of metastasis? What other biological processes can be evaluated to learn more about dormancy and reactivation? Do CTCs have stem cell characteristics and gene expression signatures? Are there diagnostic markers for dormant cells that will identify whether they will be reactivated and become metastatic?

Questions asked and hypotheses derived by this group overlap significantly with the niche/microenvironment group. Coordinated efforts to understand DTC signaling and the role of the microenvironment could accelerate the creation of a diagnostic test to detect dormant versus non-dormant DTCs or niches.

Recommended Next Steps

If dormant DTCs are like stem cells and can be maintained in a dormant or stem cell like state, what can we learn from the stem cell community?

1. Identify markers of cancer stem cells that will predict whether a cell will remain dormant or will be reactivated
2. Identify druggable targets against cancer stem cell proliferation
3. Examine the existing pharmaceuticals that target pathways to maintain a stem cell state can be used clinically in breast cancer patients

Immune System

Frank Calzone, Cyrus Ghajar, Stephen Johnston, Debbie Laxague, Kim Lyerly, Shirley Mertz, Josef Penninger, Joseph Pickrell, Julia Tchou

Therapeutically targeting DTCs may be a clinically effective method to prevent the development of metastasis. This could be mediated through the activation of immune cells that destroy dormant cells or maintain a constant dormant state. Developing a clinical diagnostic test to identify dormant versus active DTCs or CTCs will inform patients of their risk of developing metastatic disease and will provide a mechanism that can be exploited to prevent the development of metastatic disease.

The focus of this group is to determine if the immune system interacts with dormant tumor cells and how can this be exploited diagnostically. Testing would be done in mouse models to gain a fundamental understanding of interactions between immune cells and dormant DTCs prior to translation into human or clinical samples.

The initial questions would focus on immune cells and dormant DTC interactions. What cells in the microenvironment are necessary for such an interaction? Studies In vivo in mouse models will look at real time interactions of T cells and dormant DTCs. Young and old mice can be used to determine if the age of the immune system is an important factor.

Recommended Next Steps

1. Establish a mouse model that mimics human disease and therapeutic regimens.
2. Determine how current therapy alters T cell-DTC interactions
3. Identify gene expression profiles in a mouse model of breast cancer that includes young and old mice as a variable. Does this profile change with treatment or latency time?

CONCLUSIONS

The Second Annual Artemis Meeting on the Prevention of Metastasis provided the time and a venue for advocates and scientists to discuss many issues surrounding breast cancer metastasis. Together, they critically analyzed new methodology and new models for studying metastasis prevention in novel ways and developed several potential research directions to pursue. Ongoing discussions will further focus, clarify and identify an approach to studying the interaction of the immune system with metastatic cells in an effort to prevent spread of the disease.