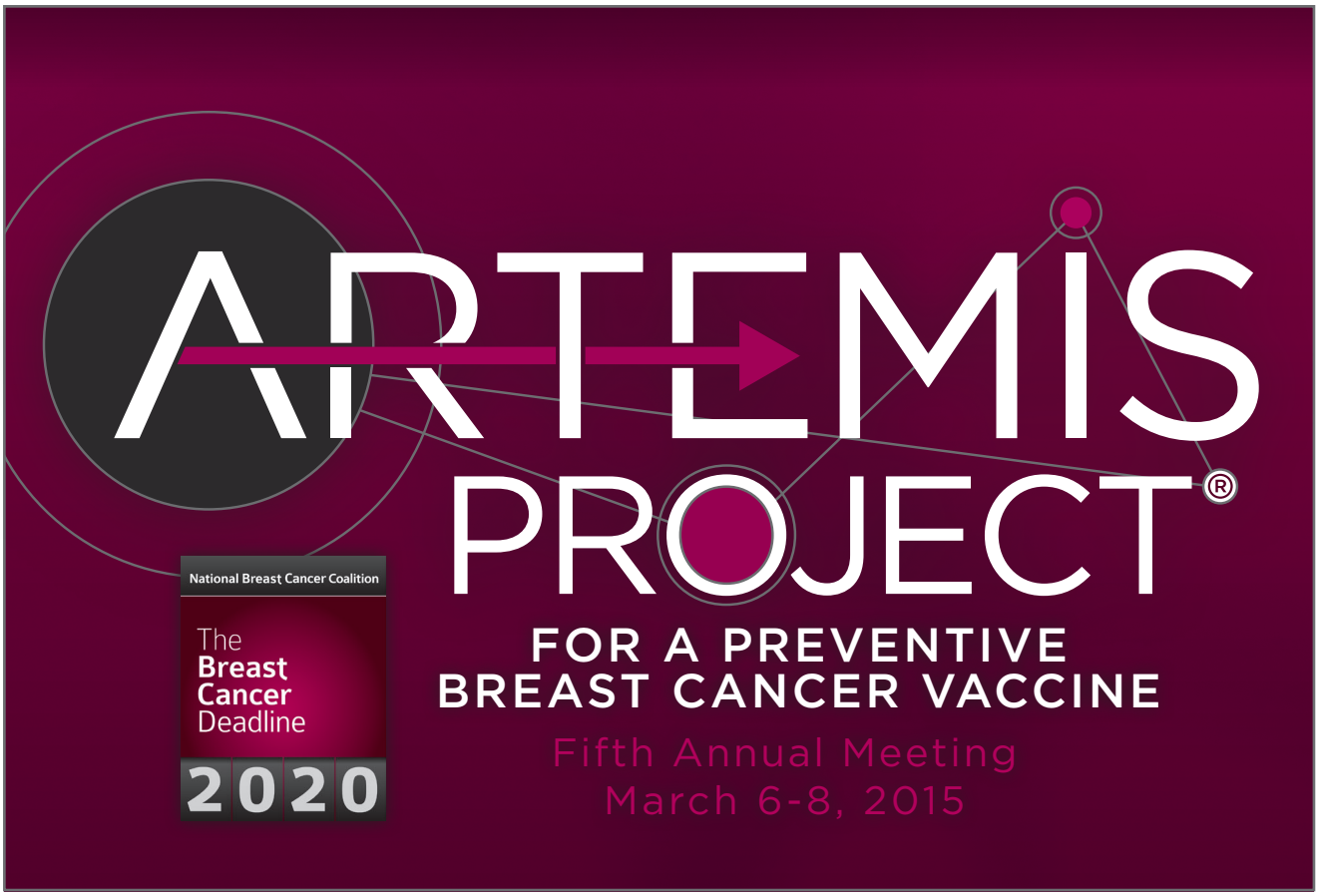

I. INTRODUCTION

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?

This report provides an update on progress made over the past year towards the development of a preventive breast cancer vaccine.

B. FIFTH ANNUAL MEETING: GOALS

The goal of the Fifth Artemis Annual Meeting for a Preventive Breast Cancer Vaccine was to identify protein targets in breast tumors that can be used to develop a preventive breast cancer vaccine for healthy women and to develop a strategic plan for vaccine creation and clinical trial development. The meeting agenda focused on antigen selection, clinical trial design, and goal setting for the next 1 – 3 years that would enable the initiation of a clinical trial by 2017.

C. 2015 ANNUAL MEETING PARTICIPANTS

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

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

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H. Kim Lyerly, MD, FACS George Barth Geller Professor for Research in Cancer and Professor of Surgery, Duke University Medical Center

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Joseph Pickrell, PhD, Junior Investigator and Core Member, New York Genome Center, Adjunct Assistant Professor, Department of Biological Sciences, Columbia University

Michele Rakoff Advocate, NBCC

Patricia Renzulli Manager, Breast Cancer Grants, National Philanthropic Trust

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Asad Umar, DVM, PhD Chief, Gastrointestinal and Other Cancers Research Group, National Cancer Institute, NIH

Fran Visco, JD President, NBCC

Douglas Wall, Founder and Managing Partner, Volcano Capital

Jason Weber, PhD, Co-Leader, Breast Cancer Research Program, Siteman Cancer Center, Co-Director, Molecular Cell Biology PhD Graduate Program, Washington University

Alana Welm, PhD Associate Member and Scott Zarrow Chair in Biomedical Research, Immunobiology & Cancer Research Program, Oklahoma Medical Research Foundation

Alice Yaker Advocate, NBCC

MEETING SUPPORT

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. BACKGROUND PRESENTATIONS & UPDATES

A. ADVOCATE UPDATES

Review of Vaccine Landscape

Debbie Laxague

A review of the clinical trial landscape over the past year revealed that most breast cancer vaccine clinical trials are still being conducted in patients with metastatic disease. Although many new trials have opened since 2014, none have tested vaccines in a population of healthy women. There are no data on the two trials that included healthy women that were reported in the media in 2014.

Her2 remains the primary target for vaccine development. Because Her2 overexpression is detected in only approximately 20% of breast cancer patients, and the Her2 vaccines are tailored to a subset of those patients who express a specific HLA protein, these trials are limited in scope.

Artemis Project: Updates Since the 2014 Meeting

Kim Lyerly

The 2014 Artemis Annual meeting established the Critical Path, a strategic framework that provides a blueprint for the development of preventive vaccine. To facilitate this process, existing methods that can be exploited to increase the speed of this work (an Accelerator Arm) were also identified. One of the essential areas identified in the Critical Path was clinical trial design and testing. To begin discussions about trial design, a Satellite Symposium, "How can we design novel trials for vaccines that prevent cancer?", was incorporated into the FDA sponsored Accelerating Anticancer Agent Development and Validation Workshop to be held in May 2015. This meeting will allow for a productive discussion with scientists, advocates, and representatives from the FDA and NCI about trial design, vaccine targets, and patient populations for the development of a breast cancer vaccine.

The National Cancer Institute Central Institutional Review Board was expanded in January 2015 to include a subsection focused on the review of cancer prevention clinical protocols. This board will set parameters for advancing preventive vaccines.

B. RESEARCH UPDATES

Artemis Project: DCIS

Kim Lyerly

Dr. Lyerly provided an update on the characterization of genetic alterations found in ductal carcinoma in situ (DCIS) and invasive carcinoma based on a research project that he and Dr. Greg Hannon have been conducting. To date, DCIS and invasive cancer samples from 30 patients have been isolated and analyzed by both whole genome and RNA sequencing to determine any genetic alteration or change in gene expression among the tumor subtypes. The goal is to develop methods to identify patients that have a tumor that will ultimately progress to invasive disease. Additional partners who can provide expertise in transcriptomics, T cell receptor analysis, and proteomics are being sought.

In a related study, Dr. Lyerly has developed a new imaging method to detect breast cancer tumors earlier, when they contain thousands instead of billions of cells. This method uses a heat shock protein 90 (Hsp90) inhibitor, Ganetespid, conjugated to a paramagnetic contrast agent. In animal models, this reagent accumulates preferentially in tumor and not in normal cells and can be imaged using near infrared imaging (NIR).

An in-depth discussion following this presentation contributed to the generation new ideas for a pilot study using stored DCIS biospecimens and potential collaborators who could be involved.

Vaccine Research Update

Stephen Johnston

Dr. Johnston presented two plans to prevent the development or progression of breast cancer using a vaccine approach. Plan A would be to develop a vaccine that is given prior to development of a tumor to stimulate a protective immune response. Plan B would identify an immune signature able to detect early stage tumors that can be used for medical monitoring of a patient. Once a tumor was detected, immunotherapy such as checkpoint inhibitors could be administered. This presentation generated a lengthy discussion about appropriate models and the use, adverse side effects, and safety of these checkpoint inhibitors in healthy individuals.

C. RESEARCH PRESENTATIONS: NEW APPROACHES

Immunotherapy Approach: Anti-PD-1/PDL1

Silvia Formenti

Dr. Formenti provided a brief overview of the mechanism of anti-PD1/PDL1 therapy. When PD1 or PDL1 expression is increased on the surface of the tumor cell, recognition of those cells by the immune system is diminished. This results in immune escape and allows tumor cells to avoid detection and death. Therapy against these proteins can effectively block the signal from PD1/PDL1 so tumor cells no longer escape recognition by the immune system and are eliminated. This strategy of restarting the immune system by blocking a negative regulator has been successfully employed as a cancer therapy, especially in melanoma cases.

Since cancer immunotherapy and the use of anti-PD1/PDL1 therapy is an emerging therapy and intense area of research for the treatment of cancers, this presentation generated a discussion among participants on its use and safety. Additionally, since this therapy is rather new, the long term exposure to these agents was of concern and an area of discussion.

Patient Explants/ Xenograft and Potential Use in Cancer Antigen Discovery

Alana Welm

Patient derived xenograft (PDX) models have been developed over the past several years as a potentially effective model for the study of human breast cancer. To inform Artemis members of the benefits and limitations of these emerging models, Alana Welm provided an update on the science surrounding their use in research. In these models, tumor samples are isolated from patients and transplanted into immunodeficient mice. While this model may be useful to study genetic characteristics and histology of the primary human tumor, there are several limitations to this system. The Luminal A subset of breast tumors has never successfully grown in PDX models. Indeed, only about 30% of all patient samples successfully grow in these mice. Growth of a human tumor in these models is not correlated with cancer stage or grade suggesting that some other factor may predict if these tumors will grow. Additionally, this model uses immunodeficient mice that prevent any analysis of the role of the immune system in tumor growth or metastasis of human tumors. It was noted that this system might be a good model to study epithelial to mesenchymal transition (EMT) involved in metastasis. Participants discussed the usefulness of this model in current Artemis work.

III. SMALL GROUP SESSIONS

Participants broke into small groups to address several issues: antigen selection; how to proceed into a clinical trial; and how to best accelerate progress in the next 1 – 3 years.

A. ANTIGEN SELECTION

Participants broke into four groups and were tasked with creating a priority list of antigens for an off-the-shelf vaccine to prevent breast cancer. These group sessions were designed to include diverse expertise and to stimulate discussion in novel ways. Participants were given the following parameters: the vaccine could include a single antigen or multiple antigens; it could be limited to a subset of breast cancers; self-antigens, neo-antigens, or both could be considered; and a rationale for the selection of antigens was required.

After reassembling and sharing the results of the breakout session discussions, all groups agreed that the antigens selected should be specific for breast tumors and not expressed in normal cells. They all also agreed that a multi-antigen vaccine that could target several subsets of breast cancer would be the most effective and beneficial. Three of the four groups identified specific antigens based on driver status, subtype expression of the protein, immunogenicity of the antigen, available preclinical data, and known genetic or molecular characterization in breast cancer samples.

After in depth and dynamic discussions, the group devised its own list that included the following potential antigen targets: Her2, hTERT, Survivin, MAGE3, Mammoglobin A, MUC1, WT1, IGFBP2, Mesothelin, AKT1, CDKn2B, CDK6, GATA3, ESR1. Together, participants refined this list further to include: Her2, hTERT, MUC1, MAGE3, Mammaglobin A, and Survivin. There was some discussion as to whether efficacy of the vaccine would be improved with concomitant anti-PD1 therapy.

There was general consensus that high risk populations should be studied first, although the vaccine should be developed for healthy women. FDA input on trial design and population will help speed the progress towards development and clinical trials.

B. PROCEEDING INTO CLINICAL TRIALS

During this session, participants broke into three groups to discuss clinical trial design, vaccine development, and antigen credentialing. Each group discussed the best method for clinical trial development. Groups were then reconvened to present ideas and to collaborate to refine their ideas.

Clinical Trial Design

During this session, there was general consensus that initial clinical trials should be conducted in patients newly diagnosed with ductal carcinoma in situ (DCIS). This group is the closest group of patients to healthy individuals and includes a subset of patients that will progress to invasive disease. The trial would be a registration trial with no randomization and a primary endpoint of local invasive disease. It is anticipated that in the absence of any vaccine, 25% of the patients would progress. A secondary outcome would be immune response that would be measured in blood. This trial would have a 5 year follow-up period. It was also recognized that there is a window of opportunity in which to test a vaccine utilizing a randomized cohort if the vaccine is given prior to surgery. This would allow for testing both the vaccine and the immune response that is generated.

Vaccine Development

A vaccine with 3 – 5 antigens would be most effective in targeting several subsets of breast cancer. Scientists could be challenged to develop a vaccine with a "Make-the-Vaccine" challenge grant. DNA, plasmids, and viral vectors (CMV or adenovirus) can be created and shared to generate preliminary safety and efficacy data in mice and macaques that would be used to initiate an FDA Investigational New Drug (IND) application.

Antigen Credentialing

A third group discussed how to validate antigen selection and inclusion in a breast cancer vaccine. Discussions centered on next steps for moving the antigen list to a vaccine product: identifying who will make the vaccine, deciding how will it be funded going forward, and determining what model system would best test vaccine safety and efficacy.

IV. HOW TO BEST ACCELERATE PROGRESS IN THE NEXT 1-3 YEARS

The last session of the meeting focused on how to accelerate progress in the next 1 – 3 years. It was suggested that clinical trials could be started by Artemis by establishing a Sponsored Research Agreement with an academic institution or using Clinical Research Organizations to contract the work. This can generate preliminary or early data that provide the rationale for larger phase 3 trials. Small trials that are conducted in metastatic patients can be initiated, followed by small trials in a healthy population and those with DCIS, culminating in a large scale preventive trial. Lastly, it was suggested that Artemis could create a tool kit of reagents that are necessary for vaccine development. This would include primers, antibodies, vectors, and cell lines that would be freely available to the research community for work on a vaccine. Any reagents created in individual labs for this project could be subsequently included in this toolkit for other investigators to use and improve upon. Artemis would then be a resource for free reagents for scientists to use to create a preventive vaccine.

Recommendations

- Hold smaller focused meetings to elaborate on the clinical plan
- Revitalize data mining group
- Discuss incorporation and IP issues with lawyers

Conclusions

During this year's Artemis meeting, experts provided an update on previous work including data from ongoing clinical trials that included healthy subject participants and efforts to sequence the genome of tumor samples from DCIS patients. Additionally, the advantages and limitations of new study models such as Patient Derived Xenograft (PDx) mouse models, vaccine development strategies, and new therapies including anti-PD1/PDL1 immunotherapy were discussed. Small group sessions facilitated the selection of six self antigens that will serve as the basis for vaccine development and discussed best methods for clinical trial design and patient participation.

The fifth Artemis Project Annual meeting marked a turning point for the Artemis project. While discussions continued about research projects and new developments in the field, important decisions about antigen selection were made. With the consensus on the antigen markers, substantive work on developing the Preventive Vaccine can now begin. Efforts to coordinate this work are currently underway.