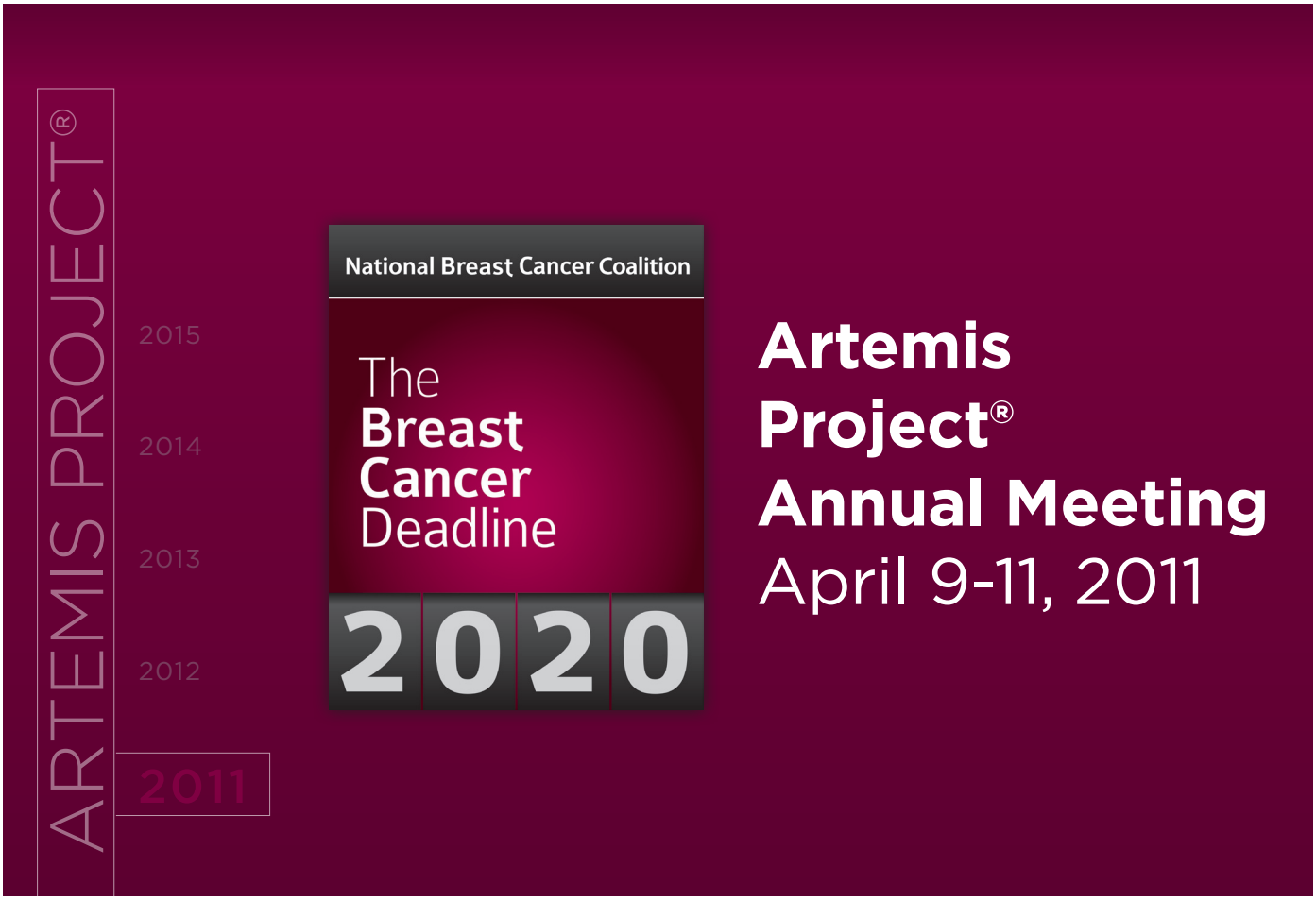

I. OVERVIEW OF PROJECT

The National Breast Cancer Coalition (NBCC) is dedicated to ending breast cancer through the power of grassroots action and advocacy. Last year, NBCC launched **Breast Cancer Deadline 2020®**—a watershed event in the history of breast cancer that will lead to the eradication of the disease by the end of the decade.

The purpose of **Breast Cancer Deadline 2020®** is to create a paradigm shift in the breast cancer world—to change the conversation and to refocus resources and efforts to the areas that will lead to the goal of ending breast cancer with a focus on two areas that do not currently receive a great deal of attention:

- ➔ Primary Prevention: How do we stop people from getting breast cancer?
- ➔ The Causes & Prevention of Metastasis: How do we stop people from dying of breast cancer?

The four specific strategies that NBCC will utilize to reach this goal are:

- Targeted research, including new research strategies and research collaborations
- A public policy approach, including federal legislation
- Grassroots advocacy and education of a large corps of activists to engage their communities
- Communications & media outreach to change the conversation to ending breast cancer by 2020

Within the research component, the central programs are strategic summits, catalytic workshops and collaborative efforts with a multi-disciplinary and diverse group of stakeholders. These programs address whether and how to proceed in areas that could have a major impact, and bring together a cross-section of stakeholders, including academic and government scientists, regulators, health care providers, researchers in biotechnology and pharmaceutical industries, and advocates. The goal is to break through the confines of the current systems that have not yet uncovered the causes of breast cancer or its spread, or have led to effective means for prevention.

The first project to arise from this work is NBCC's Artemis Project®, which brings together a collaborative group of advocates and scientists to take a strategic, systematic, yet broad approach to the design of a five-year development plan for a breast cancer preventive vaccine. Through the Artemis Project®, NBCC has created an innovative, advocate-led, mission driven model, which ensures appropriate focus on the end result. This model will be replicated to advance other identified priorities within the two key areas of primary prevention and the prevention of metastasis.

The Artemis Project® was chosen as the first focus area because the potential impact toward ending the disease is great and because recent scientific progress has created an opportunity. Increased knowledge about immunology, genomics, the molecular basis of tumor genesis and vaccine technology, including design, synthesis, and delivery, have together created an unprecedented opportunity for development of a preventive vaccine for breast cancer. A broad, systematic, collaborative approach is needed to ensure the safest, most efficacious vaccine is pursued in a timely manner.

BACKGROUND

In March, 2010, NBCC convened a catalytic workshop to determine whether a strategic approach to the development of a preventive breast cancer vaccine is feasible given the existing state of knowledge. The 17 participants reflected a broad range of expertise, including breast cancer advocacy, epidemiology, immunology, clinical cancer care, biotechnology product development, and the federal regulatory drug approval process. The group gathered for two days of roundtable discussions in Calistoga, California. A few themes emerged:

- Scientific and technological advancements in immunology and genomics provide a new rationale for the development of a preventive breast cancer vaccine.
- Feasibility depends on an unprecedented multidisciplinary collaboration including expertise in academia, industry, and public health, coordinated by strong leadership.

In August, 2010, NBCC brought together a smaller group of individuals to identify the key issues that must be addressed to move the project forward. The overall goal was resolved into four tasks that would be addressed interactively by separate working groups:

1. Identify and prioritize antigens
2. Characterize immune system responses to breast cancer
3. Develop strategies to evaluate efficacy relevant to breast cancer subtypes
4. Develop a plan to ensure safety

The NBCC is responsible for interactions within and across teams by creating an infrastructure for communication and collaboration. Advocates will be involved at every level of oversight, collaboration, and decision-making. The preventive breast cancer vaccine effort was designated as the Artemis Project®.

II. APRIL 2011 ANNUAL MEETING

The Artemis Steering Committee, Advisory Committee, and Meeting Team Leaders gathered for a meeting in Calistoga, California April 9-11, 2011 to further develop the initial research agenda with respect to the four primary research areas. In an iterative process, teams adjusted research plans in response to critiques from the entire group of scientists and advocates.

A. 2011 ANNUAL MEETING ATTENDEES

Scientists from academia and industry, including epidemiologists, immunologists, and computational biologists, as well as regulators, providers, clinicians and advocates, attended the Annual Meeting. Each of the four key areas had a scientist and an advocate designated as Project Team Leaders for the purposes of the work to be carried out during the meeting.

2011 Annual Meeting Participants

Sharon Begley, Senior Editor and Science Columnist, Newsweek

Vladimir Belyi, PhD, Assistant Professor of Medicine, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School

Nora Disis, MD, Professor, University of Washington School of Medicine

Peter Fasching, MD, PhD, Department of Medicine, Division of Hematology and Oncology, University of California at Los Angeles

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

Liz Frank, Advocate

Stephen Johnston, PhD, Director, Center for Innovations in Medicine, Biodesign Institute, Director, Biological Design Graduate Program, Arizona State University

Keith Knutson, PhD, Associate Professor, Department of Immunology, College of Medicine, Mayo Clinic

Debbie Laxague, Advocate

Susan Love, MD, President, Dr. Susan Love Research Foundation

Wanda Lucas, Advocate

H. Kim Lyerly, MD, George Barth Geller Professor of Cancer Research, Duke University Medical Center

Phillipa Marrack, PhD, Professor of Biochemistry, Molecular Biology, Immunology, and Medicine, University of Colorado Health Sciences Center

Christine Norton, Advocate

Laura Nikolaides, Director of Research & Quality Care Programs, NBCC

Samuel Nussbaum, MD, Executive Vice President, Clinical Health Policy and Chief Medical Officer, WellPoint, Inc

Joy Simha, Advocate

Fran Visco, President, NBCC

2011 Annual Meeting Project Team Leaders

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

Amy Bonoff, Advocate

Frank Calzone, PhD, Scientific Executive Director, Hematology and Oncology Research, Amgen, Inc.

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

Pat Haugen, Advocate

Peter P. Lee, MD, Associate Professor of Medicine and Hematology, Stanford University School of Medicine

Ginny Mason, Advocate

Michele Rakoff, Advocate

2011 Annual Meeting Observers

Marc Hurlbert, PhD, Executive Director, Avon Foundation Breast Cancer Crusade

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

Other attendees included Sara Collina and Aimee Near, both NBCC staff, as well as meeting facilitator, Kayla Kirsch, president of LeapFrog Consulting. We regret that the following federal employees were unable to attend due to restrictions surrounding the possible shut down of the federal government:

Doug Lowy, MD, Deputy Director, National Cancer Institute

Celia Witten, MD, PhD, Director, Office of Cellular, Tissue, and Gene Therapy, Center for Biologics Evaluation and Research, Food and Drug Administration

B. 2011 ANNUAL MEETING OUTCOME: RESEARCH AGENDAS FOR FOUR TASK AREAS

Task 1: A comprehensive genomic analysis will assess the frequency of neo-antigens generated by genetic alterations and as potential infectious or mobile genetic elements within the context of breast cancer subtype.

Task 2: State of the art platforms will be used to evaluate the selectivity and functional status of adaptive immune cells (T-cells; B-cells) with respect to the factors determining cancer risk and tumor sub-type.

Task 3: The strategy for clinical evaluation of vaccine efficacy and mechanism will depend on the early analysis of tumor genetics and immune cell profiling.

Task 4: The initial focus of the safety assessment will be to generate a consensus of key stakeholders regarding the acceptable measures of benefit and risk.

C. WORKING GROUP PROCEEDINGS AND DETAILED RESEARCH AGENDAS IN FOUR TASK AREAS

a. Group 1: Identification and Prioritization of Antigens

(Members: Greg Hannon, Vladimir Belyi, Phillipa Marrack, Amy Bonoff, Peter Fasching, Stephen Johnston, Marc Hurlbert, Wanda Lucas, Pat Renzulli, Laura Nikolaides)

i. Purpose

This team will systematically search for a virus or antigen target or targets, that will be safe, effective, and provide broad coverage for a diverse population of women. The team will methodically identify potential antigens, both foreign and self, including viruses, and neo antigens that arise from splicing. For each identified antigen, functional and historical (history of safety) information will be collected, and the opportunity for use described.

ii. Discussion Highlights and Research Agenda

After receiving feedback from large group discussions, the target group decided upon a specific research agenda that involves a multi-pronged approach of identifying an infectious agent (path A) or neo and semi-neo antigens (path B).

Path A: Infectious Agent

The key objective of the first path is to obtain evidence for or against the involvement of a pathogenic agent in breast cancer through a genomics approach and a serological (immunologic) approach. In the genomics approach, researchers will look for signatures of a virus or bacterium in the genomic DNA sequence and possibly at the RNA level, which is less costly and likely, more readily available. The serological (immunologic) approach assumes that an infectious agent would leave a trail of antibodies, and the goal is a case-control study for the presence of antibody reactivity against an infectious agent or differential host response to a known agent, with further validation of any observed association. This will involve gathering samples for each subtype (historical serum samples should be obtainable), investigating the availability of existing technology for antigen profiling, and commissioning new technology development if necessary. If the technology permits, the specificity of tumor-associated T-cells may provide a path toward the identification of an infectious agent.

A key challenge in this approach is ensuring that all breast cancer subtypes are represented. If whole genome data is not available across all subtypes, than a sequencing program should be undertaken as part of the Artemis Project®.

Path B: Neo and Semi-Neo Antigens

Genomic approach: Researchers will mine existing and ongoing genome sequencing efforts for neo antigens that arise based upon mutations (e.g. single-nucleotide variants, indels, and structural variations). At the RNA level, researchers may mine existing and accumulating RNA sequencing data for tumor-specific (tumor enriched) alternative splicing events—these may make use of novel exons, novel splice sites, or join exons of different genes in trans. This approach will require investigating the appearance of each neo/semi-neo antigen by tumor stage, and once again ensuring that each subtype is being adequately represented.

Serological approach: This approach will be used to prioritize antigens emerging from the genomic approach rather than as a method of antigen discovery, at least initially. The same antigen profiling methods described in path A will be used to investigate antibody reactivity in serum samples from case-control cohorts. The goal is again a case-control design to look for the presence of antibody activity and to correlate this exposure with presence or absence of disease. While long-term immunity often requires CD4+ cells, the target group felt that we would have better luck developing technologies that would profile CD8+ cells for numerous reasons.

T-cell approach: Researchers will screen CD8+ T-cells from tumor or blood for reactivity toward candidate antigens identified through the genomic approach. This will require new technology development to increase the throughput of the process. The goal is to integrate information on representation, staging, immune response, and major histocompatibility complex (MHC) representation to prioritize a cocktail of about 100 antigens that is effective as primary prevention but also in the recurrent setting.

Similar to path A, success of this approach will depend on a critical understanding of the normal distribution of splice variants both in different cell types and during development to avoid unanticipated safety problems. It may be advisable to investigate the basic biology that leads to alternative/trans-splicing events that lead to the production of semi-neo antigens, since this may inform risk assessments. It will also be critical to identify the correct groups for development of T-cell antigen profiling technologies and to hedge bets by funding several independent approaches.

Key challenges include addressing the specificity of neo-antigens and semi-neo antigens to tumors, finding antigens that are well represented at early disease stages, and any limitations imposed by MHC diversity on the ability to construct a cocktail that would be applicable across disease types and ethnic groups.

b. Group 2: Characterization of Immune System Responses to Breast Cancer

(Members: Peter Lee, Silvia Formenti, Keith Knutson, Ginny Mason, Chris Norton)

i. Purpose

This team will seek to increase knowledge about how the immune system responds to breast cancer with the aim of determining what the vaccine needs to accomplish. They will look at tumor immunosurveillance mechanisms, and immune dysregulation in response to breast cancer. The focus will be on identifying changes in the immune system in response to breast tumors and any variation in different types of breast cancer. The work of this group will also involve ensuring high-avidity T-cells that can kill the tumor, immunoprofiling, determining the appropriate patients for the vaccine (high-risk, BRCA positive), and selecting the right animal models to guide translation into the clinic.

ii. Discussion Highlights and Research Agenda

This team discussed ways to increase knowledge about how the immune system responds to breast cancer with the aim of determining what the vaccine needs to accomplish. Looking at tumor immunosurveillance mechanisms and immune dysregulation in response to breast cancer subtypes will be of primary importance. The focus will be on identifying changes in the immune system in response to breast tumors and any variation in different types of breast cancer. In addition, the work will look at differences in response among individuals who die of breast cancer versus long time survivors and the difference in T and B-cell repertoires among women who do not develop breast cancer, those who do, and those who are long-term survivors.

The work will begin with translation during the first year after the target group identifies antigen(s) and includes:

- Testing vector/adjuvant combinations in animal models (which will continue through year four)
- Optimizing the avidity and numbers of cytotoxic T-cells generated via genetic vaccine antigen engineering
- Determining how to best immunize, and what the optimal composition of the vaccine should be

During the first year and throughout the project through year four, the immune group will also explore a mucosal vaccine strategy to enhance natural immune surveillance. Year two of translation will look at local breast delivery and trafficking, and the development of immune system monitoring and biomarker assays. Such assays underscore the importance of small trials with surrogate end points as an early way to screen and make sure the vaccine is immunogenic.

Most of this work will run in parallel for the first four years, and by the middle of year four, all work will converge so that we are ready to manufacture the vaccine. The work will involve developing 3-5 vaccine strategies that, based on modeling, can be expected to give the best response in humans.

The ultimate goal is that by year five, the group will take up to three vaccine constructs into phase I clinical trial(s) so that the candidates can be tested against each other and the best can be taken forward to phase II and III trials.

c. Group 3: Development of Strategies to Evaluate Efficacy Relevant to Breast Cancer Subtypes

(Members: Michele Rakoff, Liz Frank, Nora Disis, Leslie Bernstein, Debbie Laxague)

i. Purpose

This team must decide the optimal time for intervention and the appropriate population. Different scenarios must be developed to evaluate efficacy in different populations. In making decisions about the target population, in considering which population is most likely to participate in clinical trials, or which route is most advantageous for regulatory approval, the goal must always be to achieve the highest impact and maximum results for those at risk of breast cancer. This team must also consider how efficacy will be evaluated; identifying endpoint(s) while recognizing that observation of an immune response is not enough. Is there a valid biomarker or surrogate endpoint to use in the evaluation of efficacy?

ii. Discussion Highlights and Research Agenda

This group will design three stages of clinical trials under the assumption that there is a vaccine ready to go. They will consider endpoints and how to estimate the benefit.

The key objective of this group is to design a clinical trial development path from the first in human testing (phase I) to the pivotal phase III clinical trial. The phase I trial will measure safety and immunogenicity, consider dosing (identify the most immunogenic dose), and collect information on other potential biomarkers. Phase II will show efficacy, and document side effects through a two-pronged approach: a single arm study in healthy women (primary prevention) and a randomized trial in women with a particular subgroup of breast cancer (secondary prevention). Phase III will be a randomized controlled clinical trial recruiting from the appropriate population of women.

For the first three years, while the preclinical and vaccine development work is being done, this group will initiate discussions with the FDA in anticipation of the phase I trial, which will begin in year four (depending on the number of vaccine approaches). In year five, the efficacy group will continue follow-up as needed for the phase I trial and initiate planning for and recruitment to a primary prevention and a secondary prevention phase II trial.

After completion of the phase II trials, during years 7-9, the goal is to initiate planning and recruitment to the phase III randomized controlled trial.

d. Group 4: Development of a Plan to Ensure Safety

(Members: Kim Lyerly, Frank Calzone, Pat Haugen, Sue Love, Joy Simha, Sam Nussbaum, Fran Visco)

i. Purpose

This team will work with the other teams to consider safety issues across all steps of the project. The vaccine safety must be proven before its efficacy. There cannot be an assumption concerning the safety of the first immune response to an exogenous agent, since, depending on the antigens used, there is the potential for autoimmune disease. Another crucial consideration is the safety of immunizing women "at risk" for pregnancy. During antigen selection and evaluation, the possibility that antigens could be present in embryos or a developing fetus, must be considered. There is also the potential for cross-reactivity secondary to prophylactic vaccination, causing an antigen reaction against normal cells with antigens similar to tumor-specific or tumor-associated antigens. These are among the many other, important safety considerations that will have to be addressed as part of any strategy on breast cancer vaccine development, before any clinical trials could begin.

ii. Discussion Highlights and Research Agenda/Workplan

The goal of the safety group is to determine the risk associated with early vaccine candidates. A key aspect of this process is gathering information, engaging the FDA to ensure that standards and requirements are being met, and recruiting a team leader. This team will also recruit an advisory board of physicians with expertise in relevant areas to review the potential list of antigens and to help determine what the safety plan/protocol should look like. All of these are tasks that can be completed during the first year.

Next, the group needs to quantify the risk associated with the candidate vaccine(s). There is acute risk and then lifetime risk (safety). Ultimately, the team will need to calculate a risk to benefit ratio. Safety should be driven by historical information from trials that have been done on other vaccines. Information will be collected on known risks for various self-antigens and viral agents.

Once there is an established vaccine construct in year two, experts will be consulted to give advice on what adjuvant(s) to use, as well as the safety profile associated with each adjuvant or combination thereof. A safety protocol will be developed for each antigen that comprises the vaccine. Next, year three will involve a clinical immunology program to monitor the immune response to the antigen(s), correlating adverse events with this response, and establishing appropriate bio-specimens for pharamacovigilance to understand why specific adverse events occur.

III. ARTEMIS PROJECT®: NEXT STEPS

The immediate next steps involve designating a project manager to oversee the work, and the creation of a detailed work plan, with particular emphasis on the target work group and the immunology group. Subsequently, seed grants will be distributed to the most appropriate working groups to begin implementing the work plans. The Artemis Steering Committee, Advisory Committee, Team Leaders and working group members will continue to gather each spring in Calistoga, California for annual meetings to assess progress, and to adjust teams, projects, and focus as necessary.

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