NATIONAL BREAST CANCER COALITION

ARTEMIS PROJECT

ANNUAL MEETINGS
MARCH 14-17, 2024

I. INTRODUCTION

The National Breast Cancer Coalition (NBCC) was formed in 1991 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 support its mission. Launched in 2010 to support the NBCC's mission-oriented research goals, the Artemis Project®, under NBCC leadership, brings together leading researchers and trained advocates who set priorities and design and implement research plans that focus on two areas:

- **Primary Prevention:** How do we stop women and men from getting breast cancer?
- **Prevention of Metastasis:** How do we stop them from dying of breast cancer?

The Artemis Project reports from previous annual meetings, found at www.stopbreastcancer.org/what-we-do/research/artemis-project/, lay out the history of the Artemis Project. This report provides a summary of discussions and recommendations made at the 2024 annual Artemis meeting. This meeting had 24 participants, including advocates and scientific expertise ranging from immunology, biomedical engineering and genetics to molecular biology, radiation oncology and clinical oncology.

2024 ANNUAL MEETING PARTICIPANTS

Michele Atlan Research Advocate and Board Member, Breast Cancer Care & Research Fund

Frank Calzone, Ph.D. Biotechnology Consultant

Christine Carpenter, Ed.S. Advocacy Chair, Beyond Pink TEAM, Cedar Valley Cancer Committee

Brandon DeKosky, Ph.D. Phillip and Susan Ragon Career Development Professor of Chemical Engineering, Massachusetts Institute of Technology

Daniel Douek, M.D., Ph.D. Chief, Human Immunology Section, Vaccine Research Center, NIAID, NIH, DHHS

Mikala Egeblad, Ph.D. Bloomberg Distinguished Professor, Johns Hopkins University

Steve Elledge, Ph.D. Gregor Mendel Professor of Genetics and Medicine, Department of Genetics, Harvard Medical School, Division of Genetics, Brigham and Women's Hospital

Yaniv Erlich, Ph.D. CEO and Co-Founder, Eleven Therapeutics

Silvia C. Formenti, M.D. Chair, Department of Radiation Oncology, Weill Cornell Medical College; Radiation Oncologist-in-Chief, New York Presbyterian/Weill Cornell Medical Center

Cyrus Ghajar, Ph.D. Director, Laboratory for the Study of Metastatic Microenvironments, PSH Program: Translational Research Program, Fred Hutchinson Cancer Research Center

Andrei Goga, M.D., Ph.D. Professor, Department of Cell and Tissue Biology, University of California San Francisco; Co-Leader, Breast Oncology Program, UCSF Helen Diller Family Comprehensive Cancer Center

Hani Goodarzi, Ph.D. Associate Professor, Department of Biophysics & Biochemistry, University of California San Francisco

Pat Haugen Advocate, Minnesota Breast Cancer Coalition

Judi Hirshfield-Bartek, R.N., M.S. Advocate, Dr. Susan Love Research Foundation

Christoph Klein, M.D. Chair of Experimental Medicine and Therapy Research, University of Regensburg

Simon Knott, Ph.D. Assistant Professor, Biomedical Sciences and Associate Director, Center of Bioinformatics and Functional Genomics, Cedars-Sinai Medical Institute

Keith L. Knutson, Ph.D. Professor, Department of Immunology, College of Medicine, Mayo Clinic; Director, Mayo Clinic Florida Cancer Research Program

Christopher Li, M.D., Ph.D. Research Professor, Epidemiology, Fred Hutchinson Cancer Research Center

H. Kim Lyerly, M.D., FACS George Barth Geller Professor of Cancer Research, Professor of Surgery, Associate Professor of Pathology and Assistant Professor of Immunology, Duke University Medical Center

Serena Nik-Zainal, Ph.D. Professor of Genomic Medicine and Bioinformatics, CRUK Advanced Clinician Scientist and Honorary Consultant in Clinical Genetics, University of Cambridge

Nimmi Ramanujam, Ph.D. Robert W. Carr Professor of Biomedical Engineering, Duke University

Michelle Tregear, Ph.D. Chief Programs Officer, National Breast Cancer Coalition

Fran Visco, J.D. President, National Breast Cancer Coalition

Alana Welm, Ph.D. Ralph E. and Willa T. Main Presidential Endowed Chair, Cancer Research, University of Utah; Senior Director of Basic Science, Huntsman Cancer Institute

Xiang (Shawn) Zhang, Ph.D. William T. Butler, M.D., Endowed Chair for Distinguished Faculty and Professor of Molecular and Cellular Biology; Associate Director, Lester and Sue Smith Breast Center; McNair Scholar; Interim Director of Breast Center, Baylor College of Medicine

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II. BACKGROUND

The Artemis meeting began Thursday evening, March 14, which was set aside for introductions, an NBCC update, Artemis' background and general scientific discussion. As is tradition, participants then began by identifying and discussing the current burning questions they believe are key in breast cancer. The meeting then moved to the session on "Primary Prevention," which was held from Friday, March 15, to noon on Saturday, March 16, followed by the session on "Prevention of Metastasis," which concluded after lunch on Sunday, March 17.

III. ARTEMIS PROJECT ON PRIMARY PREVENTION

March 15-16, 2024

BACKGROUND PRESENTATIONS

Current Capabilities and Limitations of Spatial-Profiling Technologies and What the Future Holds

Simon Knott

A decade ago, bulk DNA profiling enabled an average picture of the cells in a sample. Then, single-cell sequencing technology allowed identification of the phenotype of each cell type. Today, spatial-profiling technologies enable identification of each cellular phenotype in addition to the location of the cells, providing information on how the cells are interacting.

Simon briefly described several different types of spatial-profiling technologies, including targeted spatial proteomics, location barcoding, multiplexed fish, spatial epigenomics and imaging mass spectrometry. He then described a current spatial transcriptomics analysis of normal/premalignant breast tissue from women at high risk of developing breast cancer who are participating in a breast cancer prevention trial. Simon concluded by talking about how spatial-profiling techniques are being used to identify different cellular communities and how they can be studied to see what is guiding their different phenotypes—a process called niching.

Participants asked how the number of different cellular niches are determined and how different cell types are defined. Simon responded that niches are determined using a bootstrapping strategy in which the difference between niches is maximized, along with the stability of the niches. Participants also raised questions around data storage and sharing since the size of these datasets is enormous.

The Promise of AI in Breast Cancer: Why This Time It Is Different

Hani Goodarzi

Artificial intelligence (AI) is considered the next frontier in moving research forward and has long promised to revolutionize the world. Hani gave some background on how traditional AI models have worked and reviewed some of the more recent advances in AI that are now being used by bench researchers to propel discovery. He reviewed how, to date, there have been limited applications for machine learning (ML)/AI in medicine; the best examples have been in reading pathology slides and mammography images, where AI has been shown to be, in some instances, better than pathologists at finding anomalies. Hani noted that until recently, traditional AI has had limited impact on medicine because the available models have required large amounts of heavily annotated data that is both expensive and rare.

Foundation models have emerged in the last five years and changed these limits. Foundation models are large-scale, adaptable models that are trained on a broad dataset, including text, images and videos from the Internet. They allow for the self-supervised training of a model on unlabeled data, which is similar to the way human brains work. Hani sees three main applications of modern AI in cancer research: single-cell foundation models, small molecule foundation models and genome/

transcriptome foundation models. Examples of existing models that do this work are GeneFormer, single-cell GPT (scGPT) and Universal Cell Embeddings (UCE), and they are trained in a very similar way to large language models (LLMs).

Participants asked about how models learn to distinguish cell types and the type of training necessary to run this type of model. Participants also wanted to know how to keep a self-supervising model from learning from bad datasets, which could compromise the model's usefulness. Hani answered that models do learn batch effects, but dataset selection and guardrails are important. He also mentioned that AI hallucinations are an ongoing problem with LLMs and other models trained on general datasets and that AI foundation models are really good at context, which is everything in spatial biology.

Primary Prevention Overview

Chris Li

As of 2020, breast cancer remained the most common cancer among women in 159 out of the 180 countries surveyed, and in 110 of those countries, it was the most common cause of death among women. He noted that there is a fivefold variation in the incidence of breast cancer across the world. Remarkably, mortality is similar across the entire world despite differences in access to quality of health care. This indicates that we are treating more cancers in many parts of the world, but we are not saving lives.

Chris highlighted that while there are more risk factors identified for breast cancer than for any other cancer, no more than 55 percent of an individual's risk is explained by these risk factors. In a population of thousands of people, the models are not discrete enough to be able to point out who is very likely to get breast cancer. He also discussed the heterogeneity of known risk factors across varied breast cancer subtypes and how this further complicates the utility of available risk models, as well as possible prevention interventions.

For any primary prevention intervention, it would need to have minimal toxicity and wide acceptability. He concluded with several challenges that must be addressed to improve on our current breast cancer surveillance capabilities: Can we improve our ability to identify individuals at higher risk of clinically relevant disease (e.g., lethal disease)? Can we develop acceptable interventions that meet clinically relevant efficacy thresholds? How do we address the seeming randomness that is not well addressed by current risk models?

Participants asked about the genetic risk of breast cancer and how that impacts the models and potential for prevention. Chris answered that the models that consider genetic risk can calculate a slightly higher rate of potential risk, but it still has limited value. Participants also wanted to know if any of the models focused on lethal breast cancer prediction, to which Chris said not much research has focused on predicting lethal breast cancer cases.

Review of the Vaccine Landscape and Discussion

Michelle Tregear

Every year since 2012, an advocate has reviewed the breast cancer vaccine landscape over the past year (e.g., new trials opened since the prior Artemis meeting and/or new information available from ongoing primary prevention breast cancer vaccine trials). Michelle presented the results of one of the two new breast cancer prevention vaccines. The alpha-lactalbumin vaccine with Zymosan for triple-negative breast cancer (TNBC) from the Cleveland Clinic released early Phase 1 dosing data at the 2023 San Antonio Breast Cancer Symposium. The investigators found that the lowest dose tested was the maximum tolerated dose. The vaccine is moving into a healthy, high-risk population of BRCA1, BRCA2 and PALB2 carriers, as well as into patients receiving postoperative pembrolizumab with residual disease after neoadjuvant chemoimmunotherapy.

Michelle also presented on the new treatment vaccines that registered with www.ClinicalTrials.gov in the past year, including a Phase 1 intratumoral Fluzone Quadrivalent vaccine; a Phase 1 vaccine targeting MUC1 in conjunction with neoadjuvant aromatase inhibitor in ductal carcinoma in situ (DCIS); a Phase 1/2 personalized vaccine, ConvitVax, in low-resource environments for metastatic breast cancer; a Phase 1 dose-escalation trial of a dendritic cell vaccine in metastatic breast cancer patients with leptomeningeal disease; and a Phase 1 trial of a personalized dendritic cell vaccine after surgery in early stage TNBC. Michelle also reviewed a secondary prevention cancer vaccine trial in melanoma, KEYNOTE-942.

Participants discussed the dose-limiting toxicities found by the Cleveland Clinic, which were two category 3 adverse skin reactions. The group also discussed the KEYNOTE-942 study results.

Seed Grant Update: Prevention Vaccine Project Update

Keith Knutson

Keith presented a brief update of this year's progress on the Artemis breast cancer prevention vaccine. He reviewed how the vaccine started at an early Artemis meeting and is now in manufacturing for the MVA and plasmid bases of the vaccine through the NCI PREVENT program.

Keith also shared that despite the delays resulting from the pandemic, manufacturing is now moving forward, and the extra time has been used to design the Phase 1 clinical trial. The clinical trial will involve four sites, all of which are ready to be activated as soon as vaccine manufacturing is complete and the protocol receives Institutional Review Board (IRB) approval. Participants discussed the clinical trial patient population to be enrolled, the samples that will be collected from the participants and how immunogenicity will be evaluated.

WORKING GROUP TOPICS, DISCUSSIONS AND ACTION PLANS FOR THE NEXT 12-18 MONTHS

After discussion and debate, participants agreed on four primary prevention topics for working-group activities. The groups were chosen and convened to discuss each topic, followed by large-group discussion and subsequent small-group discussion. Working groups then outlined 12- to 18-month action plans, where possible, for each topic area.

Next-Generation Breast Cancer Risk Prediction/Vaccine Prevention Trial Design

Frank Calzone, Mikala Egeblad, Yaniv Erlich, Silvia Formenti, Pat Haugen, Simon Knott, Keith Knutson, Christopher Li, Xiang (Shawn) Zhang

Considering Chris Li's presentation on known breast cancer risk factors and the inadequacy of current breast cancer risk prediction models, this group discussed whether AI could help create a smarter risk prediction model at the individual level, as well as how to identify a high-risk breast cancer population for a Phase 2 primary prevention vaccine trial if the Phase 1 safety trial proves to be safe and demonstrates immunogenicity.

For the Phase 2 trial population, participants debated selecting for only one subtype of breast cancer versus selecting individuals with a high risk of any type of breast cancer. Populations at high risk of breast cancer include BRCA mutation carriers, familial breast cancer, polygenic risk scores in the top 5 percent and women with benign breast disease (BBD). The group also discussed possible locations where the trial might be conducted to leverage settings with national health systems in place and where a smaller fraction of high-risk patients undergo prophylactic mastectomies.

In addition, the group discussed creating a new prediction model from scratch: Since current models are simplistic, how would we build an AI foundation model with more sophisticated inputs? What would the data limitations be? The group decided it would need to analyze risk factors by subtype, and the data inputs would need to be unbiased, like extracting electronic health record (her) hospital visit data from family members of women who did or did not get breast cancer, as well as including predictors of biological age, longitudinal measurements of hormones and markers of immunological fitness. Several existing biobanks were discussed.

During large-group discussion, participants noted that across Europe and the UK, there are cancer registries that might provide easy access to patients. This could also be a possible strategy for selecting patients in a future Phase 2 vaccine trial.

ACTION PLAN: NEXT 12-18 MONTHS

Aim 1: Design a vaccine prevention trial.

- Develop a trial design/protocol.
- Define patient populations for follow-up prevention vaccine studies.

Aim 2: Next-Generation Breast Cancer Risk Prediction: Fine-tune models for different subtypes of breast cancer.

- Identify new data sources.

Artificial Intelligence Discussions: Get on the A(I) Train, Move Over Rover & A(I) A(I) Captain

Frank Calzone, Christine Carpenter, Steve Elledge, Hani Goodarzi, Judi Hirshfield-Bartek, H. Kim Lyerly, Serena Nik-Zainal, Nimmi Ramanujam

The potential for AI is enormous. However, everything in AI depends on the dataset. This group focused on the question that, given a perfect dataset, what questions should we be asking considering new AI tools?

Aim 1: Utilize AI to move the progress toward preventing breast cancer forward faster.

Aim 2: Determine people at high risk of breast cancer and of lethal breast cancer to be able to take preventive measures.

To address the above aims, three projects—of varying levels of difficulty and potential given the current technology—were discussed:

1. **Get on the A(I) Train:** What germline mutations may lead to lethal breast cancer?

   The group was interested in germline determinants of breast cancer progression and breast cancer-related death and discussed the idea of using data from large databases that have been previously collected, such as DNA.Land, to identify genomic markers of lethal or nonlethal breast cancer.

   ACTION PLAN: NEXT 12-18 MONTHS

   Aim 1: Use DNA.Land data to train an AI model to find any potential germline mutations leading to lethal breast cancer.

   Aim 2: Test the trained AI model on a larger, unrelated germline genetic database.

2. **Move Over Rover:** Conduct an AI analysis of clonal competition/clonal expansion in the development of premalignant tissue to assess risk of progression.

   ACTION PLAN: NEXT 12-18 MONTHS

   Aim 1: Conduct an AI analysis using existing data of clonal competition in well-established models and consider novel preclinical models or clinical windows of opportunity.

   Aim 2: Simultaneously work on producing more data for assessment.

3. **A(I) A(I) Captain:** Conduct an AI analysis of the loss of tumor-suppressor genes/gene silencing in preinvasive transition to create targeted events. The technology for this project currently does not exist.

   The group agreed that opportunities for AI need to be considered, including what the feasible approaches are now and what the group would like to see incorporated in the future. The group also agreed that where additional datasets will be coming from is of critical importance to guarantee data quality and, therefore, quality answers.

Homeost(AI)sis: Understanding Breast Developmental States to Prevent Breast Cancer Formation

Michele Atlan, Cyrus Ghajar, Andrei Goga, and Hani Goodarzi

The homeost(AI)sis breakout group brainstormed if/how AI could be trained on large datasets from developmental biology and settings where cells are perturbed, with the goals of identifying what allows epithelium to be so robust in the face of various perturbations, as well as how things can be reversed once set down an oncogenic path. A large part of the discussion focused on what type of datasets are likely already available that could be used to train AI models.

The major conclusion of the discussion is that AI models are not currently capable of incorporating the type of perturbation data that the group identified as being important for addressing the question at hand, pushing the timeline further into the future than the typical 12-18 months. However, there are some preliminary steps the group could take while the AI models are advancing, using traditional laboratory methods and single-cell sequencing.

During large-group discussion, specific mouse and rat models were mentioned as possible starting points. The group agreed that information from multiple organs would be useful to reach any conclusions, but it was also suggested that the group start in the breast and then move on to comparisons with other organs for practical purposes.

Next Steps:

Once an initial AI model is developed, all the perturbations discussed would be fed into the model, taking approximately an additional 12 months, which would then be followed by experimental testing of the model predictions. Overall, it was estimated that the project would take around five years, since the AI technology needed is still being developed.

Bee Yourself!

Brandon DeKosky, Daniel Douek, Steve Elledge, Cyrus Ghajar, Christoph Klein, Simon Knott, Serena Nik-Zainal, Nimmi Ramanujam, Michelle Tregear, Alana Welm

The group focused on potentiating preexisting immune responses with immune adjuvants to clear mutant cells prior to the formation of a tumor, aiming to understand when the early recognition of mutant cells occurs and how the

immune system can tolerate the presence of mutant cells. The group also focused on the idea of augmenting the existing anti-cancer immune response with immune adjuvants prior to the formation of an established immunosuppressive microenvironment within the tumor. Identification of cancer-reactive antibodies may provide a further diagnostic avenue, as these antibodies may be useful to monitor disease progression.

The group discussed which adjuvant might be best to include in this approach, determining that an array of adjuvants should be tested, as well as the methodologies that could allow for the longitudinal monitoring of mutant cell frequencies in a clinical cohort. The large group noted some limitations of the proposed study, including that the duct, in general, has very few immune cells, which brings into question whether adjuvants may cause more rigorous surveillance of the tissue. The large group also discussed the ability of this work to be translated.

ACTION PLAN: NEXT 12-18 MONTHS

Aim 1: Provide proof of principle mouse study.

- Mouse with the Green Fluorescent Protein (GFP) model – Test adjuvants as a first pass to see what can eliminate the GFP protein efficiently.
- Mouse with the mutant EGFR or PI3K or other cancer protein – Optimize adjuvants.

Aim 2: Design a human study.

Long-Term Plan

A subsequent, small clinical study could be done in BRCA1/2 patients preparing to undergo prophylactic mastectomy. Since this study would require proof-of-principle data from the murine studies, it cannot be achieved in the next 12-18 months.

A third phase of this work would involve identifying tumor targeting antibodies that could also be used for diagnostic and treatment purposes.

IV. ARTEMIS PROJECT ON PREVENTION OF METASTASIS

March 16-17, 2024

BACKGROUND PRESENTATIONS

Seed Grant Update: Relative Scarcity Allows Disseminated Tumor Cells to Evade Immune Recognition

Cyrus Ghajar

The project explored how engineered T cells interact with disseminated tumor cells (DTCs) and whether they can effectively recognize and kill them. Initially, Cyrus' lab discovered that GFP acts as a strong neoantigen in mice, causing tumor regression. They identified and tracked GFP-specific T cells using tetramers and ELIspot assays, confirming that these T cells were responsible for tumor rejection. His lab used this finding as an opportunity to explore how DTCs evade the immune system.

Despite T cells' ability to reject tumors and prevent their recurrence in mice, DTCs expressing GFP persisted, indicating possible immune evasion. Further experiments showed that rechallenging mice with GFP-positive tumors resulted in rejection by the immune system, yet GFP-positive DTCs remained, suggesting that their rarity and the scarcity of antigen-specific T cells might be what contributes to their survival.

To test this, Cyrus' lab injected tumor cells into mice and then introduced varying doses of GFP-specific T cells, finding a strong negative correlation between T-cell numbers and DTCs. The study also aimed to optimize T-cell trafficking to DTCs, investigating whether the niches occupied by DTCs, and their characteristics, influence immune evasion.

Cyrus explained that his lab, in collaboration with other Artemis participants, is currently conducting the DUET study to explore these properties in patients with breast cancer. The goal is to study DTC transcriptomes, identifying specific markers as potential targets for CAR T-cell therapy or other immune-based approaches.

Key takeaways from the project to date include:

1. Immune evasion appears to be a numbers game.
2. Niches are important and may alter immune function.
3. Tissue specificity may play a role as well.

Further work will explore the transition from immune evasion to immune suppression, whether

DTCs in the lymph node induce a broader tolerance and what role DTCs in the lymph node play.

The large group discussed where the reservoirs of premetastatic cells might be located. There were several questions related to the MHC downregulation in the DTCs.

WORKING GROUP TOPICS, DISCUSSIONS AND ACTION PLANS FOR THE NEXT 12-18 MONTHS

Three metastases prevention topics were identified for the breakout discussions.

AI (and DTCs)

Michele Atlan, Frank Calzone, Yaniv Erlich, Hani Goodarzi, Pat Haugen, Keith Knutson, Alana Welm

This group discussed ways in which AI could potentially be used to gain new insight into the process of a disseminated tumor cell becoming a clinically detectable metastasis. A key question discussed was to what extent does the microenvironment dictate the phenotype of a DTC or micrometastasis and its subsequent outgrowth to overt metastasis. A second key question centered on what datasets could be used to train AI models to uncover new relationships between DTCs/micrometastases and their environment. Large datasets from these fields could be used initially to develop and train a foundational AI model, which could then be fine-tuned using smaller datasets from rapid autopsy studies.

The large group also discussed how to improve productivity in rapid autopsy programs. The consensus was that there would need to be major advances in robotics because identifying DTCs currently is a very difficult process.

ACTION PLAN:

No specific timeline was established for this project, as current AI models are not yet advanced enough. However, the action items listed below were identified to move the project forward:

Aim 1: Collate data for AI models to be trained on so that the datasets are ready when a model is ready.

Aim 2: Collect additional tissue from other rapid autopsy programs.

Wake Up or Stay Dormant

Christine Carpenter, Mikala Egeblad, Silvia Formenti, Andrei Goga, Nimmi Ramanujam, Michelle Tregear, Xiang (Shawn) Zhang

Group discussion focused on how to improve treatment for patients likely to have DTCs or who are at high risk of developing overt metastasis. Among patients with TNBC, up to 60 percent have a pathologic complete response ([pCR]; no clinically detectable residual disease) after primary treatment, and yet 10-15 percent of these individuals will still develop metastases, usually within five years. In contrast, among patients with estrogen-receptor positive (ER+)/progesterone-receptor positive (PR+) breast cancer, only about 5 percent achieve a pCR to neoadjuvant treatment, yet a smaller percent of these patients develop metastasis despite a steadily increasing risk of recurrence over what could be a 20- to 30-year time frame to relapse.

One reason for this difference is that TNBC is thought to be a more proliferative disease. Given that chemotherapy targets cycling cells, the group considered whether there might be a role for pushing DTCs into a more proliferative state that would make them more vulnerable to treatment. However, there are node-positive patients with DTCs in the bone marrow and liver who never go on to develop overt metastasis. This suggests that there is something about these patients' immune system that is keeping cancer cells in check.

There is evidence that stress may trigger dormant cells to awaken. A known example of this mechanism is the clinical manifestation of shingles from the herpes virus, which otherwise (after a chickenpox infection) remains quiescent in the ganglia of the spine, staying dormant until the individual is stressed. A similar process may take place in the outgrowth of DTCs. These mechanisms that trigger the awakening of the herpes virus may share something (i.e., a signature) that precedes the awakening of DTCs. The group also discussed the need to define the temporal and biological characteristics of DTCs before metastasis to enable opportunities for interventions aimed at preventing their clinical appearance at the earliest stages before overt metastatic outgrowth, as well as the different models that could be used to test both strategies (awakening DTCs or maintaining a state of dormancy). Sam Silverstein's work on immune fitness was also cited, and the group hypothesized that if T cells and endogenous

steroids are mediators of maintaining or disrupting dormancy, they should be targeted to enable the body to prevent metastasis.

In the large-group discussion, concerns were raised about waking dormant cells since patients are likely to have both indolent and active micrometastases, as well as it could make metastasis worse by clearing space and giving the advantage to other DTCs. It was further pointed out that this work may also learn from the field of infectious disease, including approaches studied in HIV. The idea of waking up cells seems very similar to how growth factors have been used in the past in infectious disease research, and we should learn from the results of those existing studies.

ACTION PLAN: NEXT 12-18 MONTHS

Aim 1: Convert DTCs/early disseminated metastasis to be drug-sensitive.

- Identify specific targets and vulnerabilities to make early metastasis druggable.
- Employ advanced imaging to read out new features of metastasis.
- Conduct a multiomic analysis of blood and DTC biomarkers.

Aim 2: Detect reemerging DTCs early before overt metastasis.

- Identify new methods for the detection of minimum residual disease.
- Define the signature of whether DTCs are lethal or nonlethal.
- Intervene early in metastasis; eliminate before it becomes an issue.
- Define new types of clinical trials for metastasis prevention.

The Anti-Metastatic Niche and Metastatic Niche (We Go Both Ways: Part 2)

Brandon DeKosky, Daniel Douek, Steve Elledge, Cyrus Ghajar, Judi Hirshfield-Bartek, Christoph Klein, Simon Knott, Christopher Li, H. Kim Lyerly, Serena Nik-Zainal

Aim 1: Profile matched primaries, DTCs, and metastases with spatial technology.

Aim 2: Profile the interaction between the DTC phenotype and its niche.

What is different about the DTC niche that gives rise to metastases, as compared to the niche of a DTC that never metastasizes? Multiple lines of evidence suggest that DTCs adopt a phenotype similar to cells that normally reside in the tissue they colonize. The longer a cell remains dormant, the less likely it is to ever cause metastatic recurrence. The group largely agreed that a metastatic niche is the result of cooperation or matching between specific DTC-intrinsic characteristics and the niche components. There was broad agreement that spatial-profiling technologies should be employed to profile the niche of DTCs, likely combining data from murine studies, as well as primary clinical specimens.

The large group also discussed the stability of niches and how the presence of the tumor alters those niches, as well as including other cancer types in the research to inform understanding of different niches and the role of metabolism in the consistency of niche states.

ACTION PLAN: NEXT 12-18 MONTHS

The goal for this group largely revolved around ongoing studies. Collaboration between the participants would lead to the identification of patterns that could be used therapeutically.

V. CONCLUSION

More than a decade into its existence, the Artemis Project has fostered the establishment of numerous fruitful and long-lasting collaborations among diverse researchers and advocates who would have likely otherwise never have crossed paths. The annual meetings continue to generate bold ideas and work plans on novel approaches for preventing breast cancer and preventing metastasis, many of which are brought to life through collaborative research efforts throughout the year.

Artemis continues to make progress on a preventive vaccine for breast cancer. In 2020, NBCC's proposal was accepted by the National Cancer Institute's (NCI's) PREVENT program to advance the vaccine to a Phase 1 clinical trial with manufacturing support. Though progress has been slowed because of the COVID-19 pandemic, the manufacturing of the vaccine for use in a clinical trial is currently underway; a clear path has been outlined for the Phase I safety trial; and the project is poised to move forward.

This year, in primary prevention, distinct topics that were explored included risk prediction and reduction strategies, as well as how to best utilize current and future tools and technologies, including AI models, to prevent breast cancer. During the Artemis Meeting for the Prevention of Metastasis, determining the body's mechanisms to induce inhospitable tumor environments continued as a key theme, as well as ways to mobilize and destroy latent DTCs and/or to keep them quiescent. The group also spent time discussing the state of science and exploring how emerging advancements might be leveraged and incorporated into the goals of the Artemis Project: to prevent breast cancer and to end breast cancer deaths.

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