BANBURY CENTER REPORTS

Preventing BRCA-related cancer: A think tank for innovative strategies, milestone objectives and research priorities

Banbury Center, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, USA
November 11-13, 2015

Organizers:
Alan Ashworth, University of California, San Francisco, USA
Lawrence Brody, National Human Genome Research Institute, USA
Thomas Bock, HeritX, Inc., USA

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BACKGROUND

Inherited mutations in the BRCA genes are the most prominent of the inherited cancer genes, a carrier of a BRCA mutation having a vastly increased risk of not only one but several types of cancer, including breast, ovarian, pancreatic, prostate and skin cancer.

Today's therapeutic strategies are focused on treating cancer after it occurs and the prevention approaches available for BRCA cancers are limited to surgical removal--at a young age--of organs, e.g., breasts and ovaries. This is physically traumatic, feasible for only some cancer types, and unacceptable as a standard of care for children and future generations.

We have an opportunity to develop new preventative approaches because we know underlying gene mutations leading to inherited BRCA cancers. This offers the opportunity of identifying mutation carriers for investigation and to focus research on stopping cancer before it starts.

This conference was organized to find a pathway for changing the fate of children inheriting mutated genes, so that affected families will regain a legacy of health through the development of a medical therapy that prevents all inherited BRCA cancers and leaves people healthy and whole.

The assembled researchers were asked to review the current state of knowledge about inherited BRCA cancers and challenged to devise possible non-surgical prevention strategies for BRCA cancers. The attendees were invited to create specific action items to accelerate progress that HeritX can move forward through commissioning of research targeted to these action items.

The specific focuses of this conference were: (1) alignment on the targeted profile of the therapy for preventing inherited BRCA cancer; (2) creation of research strategies to develop such a preventive therapy; (3) definition of the initial milestone objectives leading to a FDA-approvable prevention; and (4) identification of acceleration opportunities and potential hurdles to address early on.

DETAIL

The participants in this two-and-one-half day meeting included individuals carrying BRCA gene mutations as well as a balanced mix of basic researchers and drug development experts from academic, pharmaceutical, biotech and FDA backgrounds. The discussions led to an alignment on

the goal of BRCA prevention, identification of possible prevention strategies and research needed to achieve these strategies, and opportunities to be pursued in order to speed the crucial research programs.

Alignment on goal

A moderated patient session including a panel of male and female BRCA patients increased recognition of true medical need of BRCA families. This session provided an "A-ha!" moment for the research participants, focusing their attention on the need for comprehensive non-surgical prevention for these patients. One participant said this was "the most eye-opening session ever in this field." By the close of the opening session all participants had aligned around the urgent need for research that truly focuses on non-surgical prevention for all types of inherited BRCA cancer.

The attendees achieved specific alignment on existing research knowledge gaps as well as the need for accelerated progress in filling these gaps. Fundamental issues important to finding a prevention strategy and requiring experimental elucidation are: (1) to determine if BRCA carriers are inherently haplo-insufficient a state where modestly lower levels of BRCA expression contributes to the increased cancer risk. If haplo-insufficiency is a factor, the group called for work to define the level of gene expression needed to establish a wild-type condition; (2) to determine the criticality of loss of heterozygosity (LOH) as a causal event in cancer formation; and (3) to assess the role of homologous recombination as a driver of tumor initiation.

Specific commitments to move forward with research on identified knowledge gaps were made by a number of participants including those currently in the BRCA field as wells as research leaders currently outside the BRCA field.

Identification of BRCA strategies and initial steps forward

Eight potential research strategies were identified. Of these, four are being considered as initial targets: (1) Reconstitution of the wild-type BRCA gene function; (2) Increasing expression of other DNA repair mechanisms to compensate the loss of one copy of the BRCA gene; (3) Providing the gene product(s) necessary to restore DNA repair to the wild-type condition exogenously; and (4) Protecting a BRCA carrier from the earliest steps of cancer development through vaccine/immunotherapeutic approaches.

The first specific research questions, projects and milestones were defined for these prevention strategies, and researchers agreed on the research priorities. The areas chosen for immediate research focus were to: (1) Identify the earliest cellular changes leading to BRCA cancers; (2) validate homologous recombination as the primary culprit for the BRCA-related cancer risk increase; (3) Determine the criticality of loss of heterozygosity (LOH) for the BRCA-related cancer risk increase; (4) Discover means to eliminate the haplo-insufficient condition; e.g., increase the expression of the wild-type BRCA copy in order to induce genomic stability; (5) Determine the optimal level of BRCA expression required to ensure genomic health; (6) Identify modifier genes for BRCA gene expression and cancer risk.

Opportunities to speed research

Opportunities to speed research included (1) designing ways to speed availability of tissue samples for research, (2) enhancing access to existing databases and tissue collections to expedite the start of research, and (3) facilitate the exchange of information among those involved with the HeritX global research initiative.

MEETING SESSIONS

Session 1: Defining the Goal of Preventing Inherited Cancer
Chair: Thomas Bock, HeritX, Chester, New Jersey

Thomas Bock, HeritX, Inc., Chester, New Jersey, USA
Alan Ashworth, University of California Cancer Center, San Francisco, California, USA
Lawrence Brody, National Human Genome Research Institute, NIH, Bethesda, Maryland, USA
The HeritX global research initiative for preventing inherited cancer

Douglas Hager, HeritX, Chester, New Jersey, USA
Integrated R&D planning leads to faster patient benefit; Aligning on the integrated R&D process: Defining the therapeutic goal, identifying key barriers to be addressed, and specifying immediate next steps.

Joi Morris (facilitator), HeritX, Inc., Santa Monica, California
Irina Bock, Chester, New Jersey, USA
Pamela Munster, University of California, San Francisco, California, USA
Matthew Unger, Los Angeles, California, USA
Eliminating the need of affected families: Learning first-hand how BRCA affects patients and families, and recognize the remaining needs despite preventive surgery.

Douglas Hager, HeritX, Inc., Chester, New Jersey, USA
Translating the patient goal into a Target Therapy Profile for preventing BRCA-related inherited cancers: Key elements of a Target Therapy Profile for a medical, non-surgical intervention that prevents BRCA-related cancers and leaves people healthy and whole.

Session 2: How Can We Accomplish a Prevention of All Types of BRCA-related Inherited Cancer?
Chairs: Lawrence Brody, National Human Genome Research Institute, NIH, Bethesda, Maryland, USA and Thomas Bock, HeritX, Inc., Chester, New Jersey, USA

Ralph Scully, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA
BRCA Overview: The Genes, Proteins, and their cellular roles

Maynard Olsen, University of Washington, Port Orford, Oregon, USA
Tackling Seemingly Insurmountable Scientific Challenges: "Think Different!"

(Facilitators) Lawrence Brody, National Human Genome Research Institute, Bethesda, Maryland, USA and Williams Foulkes, Montreal General Hospital, Quebec, Canada
Breakout groups: BRCA Prevention Strategies: Fix, Provide, Protect and others?
Define the first milestone objectives for an R&D plan for each strategy

Session 3: Overcoming Current Hurdles. The Biology of Risk: Identifying the first steps of cancer development in heterozygous BRCA mutation carriers for therapeutic targeting
Chairs: Bruce Ponder, CRUK Cambridge Institute, United Kingdom and Alan Ashworth, University of California, San Francisco, California, USA

Joan Brugge, Harvard Medical School, Boston, Massachusetts, USA
Research strategies to identify early steps in pathogenesis

Paul Spellman, Oregon Health & Science University, Oregon, USA
Technology to pursue these strategies in healthy BRCA carriers

Session 4: Pre-empting Future Hurdles: Surrogate Endpoints: Developing candidate therapies faster
Chairs: Judy Garber, Dana-Farber Cancer Institute, Boston, Massachusetts and David Parkinson, New Enterprise Associates, Palo Alto, California

Susan Domchek, University of Pennsylvania, Philadelphia, Pennsylvania, USA
Research strategies: Identifying biomarkers or bio-signatures that could become surrogate endpoints

Judy Garber, Dana-Farber Cancer Institute, Boston, Massachusetts, USA
Non-cancer manifestations in BRCA carriers: Do they exist? Are they clinically meaningful? How to study?

Session 5: Implementing Outcomes after Banbury
Chair: Thomas Bock, HeritX, Chester, New Jersey, USA

Alan Ashworth, University of California Cancer Center, San Francisco, California, USA
Lawrence Brody, National Human Genome Research Institute, Bethesda, Maryland, USA
Summarize next steps, align on how outcomes can be implemented most effectively

MEETING PARTICIPANTS

Alan Ashworth, Institute of Cancer Research, USA
Thomas Bock, HeritX, Inc., USA
Irina Bock, Chester, New Jersey, USA
Peter Campbell, University of Cambridge, United Kingdom
Susan Domchek, Basser Research Center, USA
Douglas Easton, University of Cambridge, United Kingdom
William Foulkes, Montreal General Hospital, Canada
Judy Garber, Dana-Farber Cancer Institute, USA
Roger Greenberg, University of Pennsylvania, USA
Douglas Hager, HeritX, Inc., USA
Maria Jasin, Memorial Sloan-Kettering Cancer Center, USA
Jos Jonkers, Netherlands Cancer Institute, The Netherlands
Joanne Kotsopoulos, University of Toronto, Canada
Rong Li, Johns Hopkins University, USA
Joi Morris, HeritX, Inc., USA
Pamela Munster, University of California, San Francisco, USA
Claude Nicaise, Clinical Regulatory Services, USA
Andre Nussenzweig, National Cancer Institute, USA
Maynard Olson, University of Washington, USA
David Parkinson, New Enterprise Associates, USA
Jeffrey Parvin, Ohio State University, USA
Kirk Patrick, HeritX, Inc., USA
Bruce Ponder, Cancer Research UK, United Kingdom

James Rasulo, The Walt Disney Company, USA
Ralph Scully, Harvard Medical School, USA
Shyam Sharan, National Cancer Institute, USA
Sunil Sharma, Huntsman Cancer Institute, USA
Paul Spellman, Oregon Health & Science University, USA
Matthew Unger, Los Angeles, California, USA
Jennifer Unger, Los Angeles, California, USA
Grant Williams, Williams Cancer Drug Consulting, LLC, USA