

Obstacles, Opportunities and Priorities for Advancing Metastatic Breast Cancer Research

Margaret Flowers¹, Stephanie Birkey Reffey², Shirley A. Mertz³, and Marc Hurlbert¹; for the Metastatic Breast Cancer Alliance



Abstract

In January 2016, the Metastatic Breast Cancer Alliance (the Alliance) convened a think tank of stakeholders from academia, government, industry, and patient advocacy to discuss gaps and opportunities in clinical and translational research in metastatic breast cancer. Priorities that emerged from the meeting included the following: the need for innovative preclinical model systems

to study metastatic disease; increased sharing of resources and data; collaboration across cancer care teams and scientists; bio-repositories for studies to identify biomarkers for treatment response; creation of patient registries to increase access to clinical trials and tissue procurement; and redesign of clinical trials in metastatic breast cancer. *Cancer Res*; 77(13); 3386–90. ©2017 AACR.

Background

Metastatic breast cancer (MBC) is a treatable but still incurable disease and is the cause of virtually all deaths from breast cancer. In 2017, an estimated 40,450 women and 440 men will die from the disease (1). Improving treatments and outcomes for patients with MBC will require a coordination of efforts from the research community, patient advocacy groups, industry, and government. In spite of the fact that metastasis is the primary cause of breast cancer-related deaths, a 2014 landscape analysis conducted by the Metastatic Breast Cancer Alliance (the "Alliance," <http://www.mbcalliance.org/>) found that only 7% of government and non-profit research dollars over the past decade were focused on studies in MBC (2).

The landscape analysis was followed by an MBC research "think tank" meeting in January 2016 in Dallas, TX, attended by more than 50 stakeholders from academia, industry, government, and the Alliance communities. The agenda included topics representing major gaps and barriers to advancing MBC research, including the need for:

- Validated and standardized laboratory models for MBC.
- Tissue resources, particularly matched primary and metastatic tumor tissue.
- Standardization for collection of research biospecimens (blood and tissue).
- Collaboration between clinical and basic science researchers.
- Correlative studies within clinical trials and clinical trial designs to identify biomarkers of response.
- New clinical trial endpoints.

¹Breast Cancer Research Foundation, New York, New York. ²Susan G. Komen, Dallas, Texas. ³Metastatic Breast Cancer Network, New York, New York.

Corrected online May 30, 2018.

Corresponding Author: Margaret Flowers, Breast Cancer Research Foundation, 60 E. 56th Street, 8th Floor, New York, NY 10022. Phone: 646-497-2611; Fax: 646-497-0890; E-mail: mflowers@bcrcure.org

doi: 10.1158/0008-5472.CAN-17-0232

©2017 American Association for Cancer Research.

This short report is limited in scope to highlights from the invited talks and discussions that took place during the meeting. Where applicable, references are made to published work supporting the discussion points or recommendations. It is not intended to be an in-depth review of the status of research in MBC.

Barriers and Opportunities in Laboratory and Translational Research in MBC

Experimental model systems for metastatic research

To improve patient outcomes in MBC, new biomarkers and targets are urgently needed for drug and diagnostic development. Animal models play a critical role in this process, but most of these systems were developed to study primary disease (3). There are currently no true mouse models for the holistic study of MBC. Innovation in the development of new model systems is a priority for preclinical studies to be relevant to metastatic disease. Newly developed patient-derived xenografts (PDX) have been shown to exhibit remarkable biologic and genetic fidelity to the human tumor from which they were derived (4, 5), but even these mouse avatars of human cancer have significant limitations (3, 6–8).

In vitro models play an important role in understanding the process of metastasis and can both guide and complement animal studies. Advances in cell and tissue culturing coupled to sophisticated imaging technology makes these systems invaluable in the discovery of new molecular targets for drug development, potential biomarkers to predict an individual's response to a therapy or risk of metastasis, and to test new drugs in patient tumors *ex vivo* (9).

Metastasis cannot be studied exclusively *in vitro*, however. Appropriate *in vivo* models are required to facilitate a systematic collaborative approach that will identify the most important steps in the metastatic process and accelerate discoveries to change patient outcomes. Work is being done to create inexpensive engineering devices that mimic metastatic sites by modeling biological niches (10). These can be employed to study the cell types and cellular programs driving metastasis to these sites and can inform the experiments in a matched PDX system.

Data and resource sharing

Too much preclinical research exists in institutional silos rather than benefiting the larger research community and improving outcomes for patients with MBC. There is an urgent need for data and resource sharing to accelerate the discovery of better drugs or drug combinations, to identify novel biomarkers of risk of metastasis or drug response, and to advance our understanding of the molecular underpinnings of metastasis. In fact, the initial report from the National Cancer Moonshot Blue Ribbon Panel released in September 2016 identified data sharing as an urgent priority and called for the creation of a national infrastructure for sharing and processing cancer data (11).

A universal material transfer agreement (MTA) across all major academic centers in the United States is needed to facilitate the flow of materials between institutions. The outcome of this collaboration would not only relieve a major bottleneck in interinstitution sharing of data or tissue resources, but would lead to standardized methods of samples/data collection, annotation, and archival.

Tissue/sample procurement

Most breast cancer tissue biopsies are obtained from the primary tumor or regional nodes. Although serial biopsies collected through a patient's course of treatment are ideal for identifying tumor-specific changes over time, balancing the risk of multiple biopsies with the patient benefit is a significant concern. Coupled with the complicated logistics of collection, handling, and storage of biopsies, particularly in the community setting where most patients are treated, this presents major challenges in translational research in MBC.

Patient advocates report that when properly informed, MBC patients are eager to donate biopsies, blood, or saliva, and this is supported in the literature (12–14). However, these specimens are typically collected in the context of clinical trials. Many MBC patients are excluded from clinical trials because of prior treatments, representing a significant lost opportunity for specimen collection and study. A system that provides a way for patients to donate clinical biopsies and related medical information outside of the clinical trial setting would accelerate ongoing and future research. The MBC Project (<https://www.mbcproject.org>) is one example that has demonstrated the power of social media to directly engage patients who want to contribute to research but are not part of a clinical trial (15).

Liquid biopsies are emerging as a potential noninvasive biopsy, but their clinical utility has not been fully validated in clinical trials (16–20). As liquid biopsy technology continues to be refined, it may provide an alternative to serial tissue cores in the community clinics, but issues such as sample collection, storage/handling, assay standardization, and limitations of information technology platforms need to be resolved.

Rapid autopsy programs are gaining acceptance at academic hospitals in the United States and the United Kingdom as a way to collect metastatic lesions postmortem for research. Analyses of metastatic lesions, even when procured at autopsy, can provide valuable information that could be used to identify biomarkers to predict which patients are likely to benefit from a particular therapy, as well as advance understanding of the mechanisms of resistance to a particular therapy (21–24).

Barriers and Opportunities in Clinical/Translational Research in MBC

Findings from the Alliance landscape analysis identified several barriers to clinical trials research, including a paucity of industry-led trials in new therapeutics or combinations treatments, and a "reward" system in academia that encourages single-investigator/single-institution clinical trials (2).

This status quo fails to capitalize on the potential of emerging new therapies and promising combinations or to leverage access to patients, resources, and expertise that would come from collaborative, transdisciplinary, and multi-institutional clinical trials and thus impedes the approval of potential new therapies for MBC patients.

Studies show that metastasis is druggable (25–29), and as new therapeutic targets for late stage disease emerge, clinical trial endpoints need to shift from progression-free survival to more appropriate measurements of efficacy in this patient population.

The emergence of genomically driven clinical trials, in which patients are matched to targeted therapies based on the molecular characterization of their disease, introduces a new level of complexity in clinical trial design (30). Although efforts to couple molecular characterization (i.e., cancer genomics) with drug development have been widely embraced, they have met significant challenges. Not the least of these is a lack of standardized genomics testing, complex patient consent forms, and the emergence of "boutique" clinical trials that limit patient access (30). The AURORA Initiative led by the Breast International Group is designed to address some of these challenges (31). Data from this trial will offer a resource for future research adding new insight into the molecular evolution of breast cancer in an international cohort.

Clinical trials for MBC need to consider the unique needs of this patient population and provide new treatment options for what is currently an incurable disease. Reevaluating common exclusion criteria, such as previous treatments, to make trials available to more patients and increasing clinical trial enrollment overall will be vital to the process.

Collaboration among Stakeholders

Collaboration is key to translational research and advances in the management and prevention of metastasis. Basic scientists, clinical researchers, and the clinical care team need to communicate to increase the efficiency of bioresource procurement and to ensure that information from clinical trials continues to inform research.

Translational research should follow a circular path whereby discoveries made in the laboratory are tested in clinical trials and results from clinical trials inform discovery research. A lack of communication and collaboration between clinicians and basic scientists has created a one-way street of translational science and a chasm in the path to progress.

Recommendations

Innovation in the development of new model systems

Preclinical MBC research will benefit from the development of innovative model systems, both *in vivo* and *in vitro*, as well as a better understanding of the appropriate use for existing model systems. Utilizing a computational and systems biology approach

will allow researchers to integrate information obtained from *in vitro* and *in vivo* model systems to better understand the complex phenomena of MBC. A number of companies have developed artificial intelligence systems (e.g., IBM's Watson, Flatiron Health's OncologyCloud) that are working toward this goal. Although there are early signs of success in this area, these systems remain limited by data accessibility issues.

Removing barriers to data and resource sharing

Barriers to data sharing across institutions will continue to impede progress until academia, government, and industry agree on a solution. There may be a role for the Alliance to act as a powerful advocate for action to establish a mandate for a universal MTA.

Creating a database of modeling systems (a "TCGA" for mouse models), publishing negative study results, and providing open access to laboratory protocols would remove restrictions imposed by publisher pay walls and improve research efficiency, thereby reducing costs and accelerating discovery.

Clinical/translational research

Access to patient tissue is a fundamental component of translational research, but is a difficult and complicated problem in MBC. Tissue surrogates such as liquid biopsies and rapid autopsy are gaining acceptance and may augment, or reduce the need for, serial tissue biopsies. Alternatively, commercially available tissue collection kits, such as those used by the cord blood banking industry, could serve as a prototype for sharing biosamples between the community setting and academic centers.

Patient registries may provide an opportunity to prospectively collect information from high-risk or newly diagnosed women or patients that are currently living with metastatic disease and to develop systems to study the natural history of this disease over time. The MBC Project and TAPUR (<http://www.tapur.org/>) registries may serve as models for identifying tissue, connecting patients to clinical trials and expanding education and outreach to both patients and community oncologists.

Coordinating the collection of research biopsies with scheduled clinic visits, improving communication about the use of research biopsies, and providing a way for patients to request their clinical biopsies be shared for ongoing or future research are ways to increase access to tissue resources and engage the MBC patient population.

Rethinking clinical trials in MBC

Although MBC patients are highly represented in ongoing clinical trials, the preponderance of these trials is with agents that target cell growth and proliferation, most of which prevent metastases in preclinical models, but do not shrink established lesions as monotherapy. Endpoints in metastatic clinical trials should establish whether the drug(s) hit the intended target and can prevent new metastasis or the progression of existing metastases, rather than measuring progression-free survival alone. The success in the treatment of AIDS serves as an example of how combination therapies can be an effective strategy in the treatment of complicated diseases and may be effective in MBC as well.

Although treatment of established disease to improve outcomes is a high priority, there is also an urgent need for metastasis prevention studies. The feasibility of these will require appropri-

ate surrogate endpoints, such as can be derived from correlative studies within treatment trials and well-designed preclinical studies in appropriate model systems. Other circulating factors such as tumor cells and cell-free DNA, miRNAs, or exosomes could potentially serve this need.

The following recommendations will address some of the current challenges in clinical research for MBC:

- Encourage clinical repeat biopsies for repeat characterization or biomarker testing.
- Create a national or global registry where standard of care clinical samples are linked to bioregistries so every biopsy on every patient yields information to further our understanding of the disease.
- Record outcomes of patients with actionable alterations who are not treated with the associated targeted therapy to better understand which patients do not need more than standard-of-care therapy.
- Align the biopsy strategy to the current translational objectives of the study, while considering future clinical utility.
- Invest in resources and establish systems/processes to ensure high-quality biopsy samples and optimize preservation strategies to do more with less.

The following issues should be considered in metastasis-directed therapies:

- Most metastasis-directed therapeutics prevent metastases in preclinical models. They do not shrink established lesions as monotherapy.
- More preclinical validation is needed to understand how metastasis therapy relates to standard of care in early versus resistant disease.
- Combination therapies are necessary to address the inherent heterogeneity of metastatic tumors.
- Lead agents need an appropriate trial design and appropriate endpoints.
- New metastasis prevention trial designs are needed that are not prohibitively expensive or require long follow-up for results.

Other key points are:

- Rethinking patient registries can have an enormous impact on patient tracking, biospecimen collection, and identifying patients eligible for clinical trials of targeted therapies.
- Infrastructure, coordination, and communication, both inter and intrainstitutionally, can create standards of best practices, facilitate tissue procurement, and reduce stress on the patients and the health care system.

Next Steps

Many of the recommendations that emerged from the think tank discussions align with other recent meeting reports (32, 33) as well as the priorities of the Precision Medicine Initiative, including the following recommendations of the National Cancer Moonshot Initiative Blue Ribbon Panel (BRP):

- Creation of a network for direct patient engagement.
- Therapeutic target identification to overcome drug resistance (that can promote metastatic disease).
- Creation of a national cancer data ecosystem for sharing and analysis.

- Retrospective analysis of biospecimens from patients treated with standard of care.
- Development of new enabling cancer technologies.

One priority that is noticeably absent from the BRP report is advancing the research to prevent and cure metastasis. Adding a focus on metastasis to any of the above BRP recommendations would do much to close the gaps in MBC research.

The renewed national commitment for support of cancer research presents a ripe opportunity for the Alliance to advance the priorities discussed here. Alliance members are committed to spearheading progress toward understanding of the disease and bringing awareness to the unique needs of people living with MBC and the need for better treatment options. In fact, several Alliance members or representatives from member organizations have been invited to partake in Moonshot discussions, because of their recognized commitment and leadership in patient advocacy or cancer research.

The role of the Alliance on the big issues, funding of research, data/resource sharing, collaboration, infrastructure, clinical trial design, and approval of new and repurposed drugs in MBC, is to serve as a powerful advocate voice to increase awareness and instill a sense of urgency in overcoming these barriers to have the greatest, most immediate impact on patients living with MBC.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016;66:7–30.
2. Mayer M, Hurlbert M, Thompson C, Knackmuhs V, Mertz S, Hodges KP, et al. Changing the landscape for people living with metastatic breast cancer. New York: Metastatic Breast Cancer Alliance; 2014.
3. Gould SE, Junttila MR, de Sauvage FJ. Translational value of mouse models in oncology drug development. *Nat Med* 2015; 21:431–9.
4. Bruna A, Rueda OM, Greenwood W, Batra AS, Callari M, Batra RN, et al. A biobank of breast cancer explants with preserved intratumor heterogeneity to screen anticancer compounds. *Cell* 2016; 167:260–74.
5. Eirew P, Steif A, Khattra J, Ha G, Yap D, Farahani H, et al. Dynamics of genomic clones in breast cancer patient xenografts at single-cell resolution. *Nature* 2015;518:422–6.
6. Hidalgo M, Amant F, Biankin AV, Budinská E, Byrne AT, Caldas C, et al. Patient derived xenograft models: an emerging platform for translational cancer research. *Cancer Discov* 2014;4:998–1013.
7. Sia D, Moeini A, Labgaa I, Villanueva A. The future of patient-derived tumor xenografts in cancer treatment. *Pharmacogenomics* 2015;16: 1671–83.
8. Aparicio S, Hidalgo M, Kung AL. Examining the utility of patient-derived xenograft mouse models. *Nat Rev Cancer* 2015;15:311–6.
9. Ewald AJ. Translating our insights into the cell biology of breast cancer metastasis to improve patient outcomes. Dallas, TX: MBC Alliance; 2015.
10. Chen Z, Cheng K, Walton Z, Wang Y, Ebi H, Shimamura T, et al. A murine lung cancer co-clinical trial identifies genetic modifiers of therapeutic response. *Nature* 2012;483:613–7.
11. cancer.gov/brp. Cancer Moonshot Blue Ribbon Panel Report 2016. 2016. Available from: <https://www.cancer.gov/research/key-initiatives/moon-shot-cancer-initiative/blue-ribbon-panel/blue-ribbon-panel-report-2016.pdf>.
12. MBC Alliance. MBC Alliance Research Task Force Meeting. Dallas TX: MBC Alliance; 2015.
13. Vaz-Luis I, Zeghibe CA, Frank ES, Sohl J, Washington KE, Silverman SG, et al. Prospective clinical experience with research biopsies in breast cancer patients. *Breast Cancer Res Treat* 2013;142:203–9.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

The authors acknowledge the members of the Metastatic Breast Cancer Alliance and patients living with metastatic disease, who inspired this work and the following for their support of the meeting: Lilly Oncology (Meeting support); Speakers: Andrew J. Ewald, PhD, Johns Hopkins Medical School; Yibin Kang, PhD, Princeton University; Tari King, MD, Dana-Farber/Brigham and Women's Cancer Center; Patricia Steeg, PhD, National Cancer Institute; Robert Schneider, PhD, NYU; Danny Welch, PhD, University of Kansas Cancer Center; Josh Nicholson (Notes taker), volunteers from Susan G. Komen, and all the participants of the Dallas Think Tank whose valuable input contributed to this report. We are grateful to Deborah Collyar and Dana E. Mooney for their help in preparation of this meeting report and Drs. Danny Welch, Andrew Ewald, Tari King, and Yibin Kang for their review of the report.

Grant Support

Meeting support was provided by Eli Lilly and Company to Marc Hurlbert on behalf of the Metastatic Breast Cancer Alliance.

Received January 30, 2017; revised March 28, 2017; accepted April 20, 2017; published OnlineFirst June 10, 2017.

14. Seah DS, Scott SM, Najita J, Openshaw T, Krag K, Frank E, et al. Attitudes of patients with metastatic breast cancer toward research biopsies. *Ann Oncol* 2013;24:1853–9.
15. Wagle N. The genomics of metastatic breast cancer: what are we learning? In: Proceedings of the 2016 San Antonio Breast Cancer Symposium; 2016 Dec 6–10; San Antonio, TX. Philadelphia, PA: AACR; 2016. Abstract nr CS1-1.
16. Wong HY, Park BH. Plasma tumor DNA: on your markers, get set, go! *Ann Transl Med* 2014;2:2.
17. Dawson SJ, Tsui DW, Murtaza M, Biggs H, Rueda OM, Chin SF, et al. Analysis of circulating tumor DNA to monitor metastatic breast cancer. *N Engl J Med* 2013;368:1199–209.
18. Murtaza M, Dawson SJ, Pogrebnik K, Rueda OM, Provenzano E, Grant J, et al. Multifocal clonal evolution characterized using circulating tumour DNA in a case of metastatic breast cancer. *Nat Commun* 2015;6:8760.
19. Pantel K. Blood-based analysis of circulating cell-free DNA and tumor cells for early cancer detection. *PLoS Med* 2016;13:e1002205.
20. Swanton C, Soria JC, Bardelli A, Biankin A, Caldas C, Chandralapaty S, et al. Consensus on precision medicine for metastatic cancers: a report from the MAP conference. *Ann Oncol* 2016;27:1443–8.
21. Wu JM, Fackler MJ, Halushka MK, Molavi DW, Taylor ME, Teo WW, et al. Heterogeneity of breast cancer metastases: comparison of therapeutic target expression and promoter methylation between primary tumors and their multifocal metastases. *Clin Cancer Res* 2008;14: 1938–46.
22. Wu JM, Halushka MK, Argani P. Intratumoral heterogeneity of HER-2 gene amplification and protein overexpression in breast cancer. *Hum Pathol* 2010;41:914–7.
23. Cimino-Mathews A, Hicks JL, Illei PB, Halushka MK, Fetting JH, De Marzo AM, et al. Androgen receptor expression is usually maintained in initial surgically resected breast cancer metastases but is often lost in end-stage metastases found at autopsy. *Hum Pathol* 2012;43: 1003–11.
24. Savas P, Teo ZL, Lefevre C, Flensburg C, Caramia F, Alsop K, et al. The subclonal architecture of metastatic breast cancer: results from a prospective community-based rapid autopsy program "CASCADE". *PLoS Med* 2016;13:e1002204.

25. Fizazi K, Carducci M, Smith M, Damião R, Brown J, Karsh L, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet* 2011;377:813–22.
26. Stopeck AT, Lipton A, Body JJ, Steger GG, Tonkin K, de Boer RH, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol* 2010;28:5132–9.
27. Gnant M, Pfeiler G, Dubsy PC, Hubalek M, Greil R, Jakesz R, et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2015;386:433–43.
28. Smith MR, Saad F, Coleman R, Shore N, Fizazi K, Tombal B, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet* 2012;379:39–46.
29. Lefebvre C, Bachelot T, Filleron T, Pedrero M, Campone M, Soria JC, et al. Mutational profile of metastatic breast cancers: a retrospective analysis. *PLoS Med* 2016;13:e1002201.
30. King TA. Lost in translation: barriers to translation in MBC research from laboratory research to clinical trials. Dallas, TX: MBC Alliance; 2015.
31. Zardavas D, Maetens M, Irrthum A, Goulioti T, Engelen K, Fumagalli D, et al. The AURORA initiative for metastatic breast cancer. *Br J Cancer* 2014;111:1881–7.
32. Alizadeh AA, Aranda V, Bardelli A, Blanpain C, Bock C, Borowski C, et al. Toward understanding and exploiting tumor heterogeneity. *Nat Med* 2015;21:846–53.
33. Siu LL, Lawler M, Haussler D, Knoppers BM, Lewin J, Vis DJ, et al. Facilitating a culture of responsible and effective sharing of cancer genome data. *Nat Med* 2016;22:464–71.