

A Glimmer of Hope Funding Request Revised – 2018 Priorities

& Updates on 2017 Funded Projects

Magee-Womens Hospital of UPMC and the Women's Cancer Research Center

Magee-Womens Hospital of UPMC and the Women's Cancer Research Center are grateful for A Glimmer of Hope's past grants benefitting thousands of women and their families. Advancing our clinical and research programs, together, we are working diligently to understand the immediate and complex needs of our patients. Because of our joint effort, we can provide hope, support and the best care possible.

In this proposal, our team has identified research and patient services needs and proposed strategies that enhance and foster our cutting-edge investigations and compassionate care.

Research

Benefitting Women with Metastatic Breast Cancer

(Adrian Lee, PhD, Director, Women's Cancer Research Center)

**** Background ****

A metastatic breast cancer (MBC) diagnosis is different because it *means our patients will actively deal with breast cancer for the rest of their lives.*

With MBC, the goal of treatment is to shrink or weaken the cancer, manage symptoms and side effects, and prevent the cancer from spreading further. Changes in treatment are made as the cancer grows or spreads to new places in the body. The patient and their doctors talk regularly about progression, the growth of tumors or spread of cancer, and regression, decreases in tumor size or the cancer's reach. When one treatment stops working, they will look at new options.

Generous support from GOH has enabled our MBC research team to study and generate preliminary data regarding the effectiveness of liquid biopsy as an innovative strategy to evaluate tumors. The generosity of GOH also has provided a patient navigator to connect breast cancer patients with the services they need, and a research navigator to help them gain access to clinical trials.

**** Liquid Biopsy Research Projects ****

The Significance of Liquid Biopsies

Current treatment decisions are based mainly on the tumor's phenotype, such as hormone and/or (HER2) status assessed during the primary diagnosis. As these tumor characteristics may change over time, further biopsies of metastatic lesions are required for additional phenotype assessment in MBC.

Liquid biopsy, which is comprised of a basic blood draw and a basic blood test from a patient, provides a less invasive and repeatable method for obtaining more precise evaluation. It provides a personalized and more effective evaluation of heterogeneity and changing tumor characteristics. The goal is to use blood-based biomarkers in lieu of relying on invasive biopsies of solid metastases to monitor disease and identify novel therapeutic targets.

In other words, liquid biopsies are a recent and promising innovation that are highly worthy of intensive study in research on MBC because MBC often spreads to places that are difficult or impossible to biopsy, like the brain and liver. But with liquid biopsies, researchers and clinicians can use this very sensitive technology to draw and examine blood from patients without taking a biopsy of the metastatic site, and they can identify mutations in DNA in patients' blood samples. Moreover, it may be possible for researchers to view changes in DNA before a metastasis is visible by other means, such as imaging.

Clinically, liquid biopsies hold strong potential to change the face of patient care in ways that give rise to more personalized, precision medicine. In studying and developing liquid biopsies, the aim is to offer a real-time perspective on how well a patient's treatment is working, as gaining this insight can help clinicians adjust their treatment recommendations for patients in real time in ways that are not yet possible today within current standards of care.

In other words, by investigating the full potential of liquid biopsies, our researchers are working toward creating the ability to look for mutations in DNA, determining whether a patient's MBC has developed resistance to treatment, and then utilizing this knowledge to help clinicians explore better alternatives and adjust the patient's course of treatment accordingly, in a more timely manner.

This is a vitally important strategy to explore because as Dr. Lee, Dr. Oesterreich and others are finding, cancer is a disease that changes over time, especially within a single patient. Cancer is constantly evolving, and researchers need to find new ways to keep up with it. In the future, liquid biopsies also may prove valuable in detecting DNA mutations and predicting metastases, or possibly for early detection or risk of cancer.

Liquid Biopsy Research Projects for Detection and Treatment of Metastatic Breast Cancer

We are in the process of developing a state-of-the-art clinical trial to test the role of liquid biopsies in advanced breast cancer management.

We are pleased to report that Glimmer of Hope's 2016 award played a vital role in helping our research team generate results that demonstrated how use of liquid biopsies ultimately impacted clinicians' decisions about improvements in treatment recommendations for MBC patients. Therefore, we would like to continue and build upon our research on liquid biopsies.

Liquid biopsies hold promise to play an important role in building a heightened awareness, enhanced sensitivity, and a greater depth of understanding regarding the presence and characteristics of cancer cells within a patient's blood, even at the most subtle levels. As highlighted in the previous section, focusing on this line of research also holds potential to help improve treatments for MBC, and possibly earlier detection of cancer as well.

How Liquid Biopsies Work

Cells which shed from the tumor and enter the vasculature or lymphatic system are known as circulating tumor cells (CTCs). Similarly, when tumor cells die, DNA is released into vasculature, and can be detected as circulating free tumor DNA (cfDNA). So CTCs and cfDNAs can be measured by drawing and testing blood from patients, which is the process that we refer to as a "liquid biopsy."

Our Next Steps in Research on Liquid Biopsies – Request for Consideration of Continued Support

A specific research project that our group is pursuing is focusing on how to detect cfDNA and CTCs in patients with MBC in order to 1) measure response to treatment, and 2) identify druggable targets that might have emerged during tumor evolution.

This research project is currently comprised of the following three components:

Aim 1: Analysis of CTCs

Though rare, recent technological advances allow for the detection and isolation of CTCs. Studies have demonstrated that studying CTCs can offer valuable insight about the biology of tumors, and it can have implications for patient prognosis, therapy selection and monitoring.

While repeatedly performing standard solid tumor biopsies is an invasive procedure which can occur at limited intervals at best, as previously noted, analysis of CTCs can be considered a “liquid biopsy.” Through a series of simple blood draws, this approach can serve as a minimally invasive, long-term way to monitor disease burden, mutation status and treatment response.

Strategy/Rationale: Building upon our preliminary studies which received support from GOH, we now plan to perform a pilot study for the identification and isolation of CTCs in patients with MBC. Since MBC often harbors estrogen receptor (ESR1) mutations that render them resistant to endocrine therapies, we are interested in determining whether CTCs may play a role in the ESR1 mutation status of the tumor.

CTCs can be monitored over the treatment course of a patient to assess the frequency of specific mutations and monitor disease progression. In order to address these questions, it is necessary for us to launch a pilot study of 10 patients to confirm that CTCs can be detected in MBC patients and then assessed for ESR1-related mutations.

Goal: If this pilot study is successful, it will allow us to move forward and take the further, necessary step of CTC monitoring and analysis in upcoming clinical trials to assess disease burden, correlate it with patient outcome, and monitor the effect of cancer therapies on specific gene mutations. Then, we will further seek to analyze CTC in order to gain biological insight into the signaling pathways that drive survival and proliferation of these rare cells, although this will be a challenging task and is expected to take significant time and effort.

Aim 2: Use of MammaSeq in cfDNA

While the technology that we have previously used to measure single mutations in cfDNA is accurate and sensitive, it is not as efficient as it could be because it can only detect one *single* mutation at a time. We need to have the ability to measure multiple genetic mutations in the same sample, at the same time; in other words, we need to be able to increase the throughput of mutation analysis in cfDNA.

Strategy/Rationale: To address this dilemma, we have recently designed a panel of genetic mutations that are frequently found in breast cancer (called “MammaSeq”). By utilizing Mamma Seq, we can greatly improve the ability to sequence genetic mutations in breast cancer in a more comprehensive, more efficient, and more impactful manner.

Goal: Moving forward, as a next step in this aspect of our research, in association with our above-mentioned research on liquid biopsies, we will work to optimize this technology and our bioinformatics pipeline so that we can use MammaSeq for the simultaneous analysis of multiple mutations in samples obtained through liquid biopsies.

Aim 3: Analysis of cancer mutations in cfDNA from patients with metastatic breast cancer

Last year, we examined the clinical use of liquid biopsies in breast cancer performed in the UPMC system. Gratefully, these studies were in part supported through Glimmer of Hope funds.

Through these studies, we demonstrated our use of liquid biopsies to identify changes in genetic make-up of patient’s tumors, after which we communicated this information to the patients’ physicians. The physicians took our data into consideration, and when appropriate, they consequently modified treatment recommendations in real time for patients in accordance with the data that we had shared. More specifically, our results showed that liquid biopsies were performed on 95 patients with advanced breast cancer, and as a result, adjustments in clinical decisions were made in nearly 30% of patients. (For more details, please refer to the enclosed update, titled “Update on Research in Utilizing Liquid Biopsies.”)

The noteworthy and innovative nature of our results is that the use of liquid biopsies in clinical care of patients with MBC is showing strong potential to help physicians save lives or extend survivorship through personalized, precision medicine.

At present, there are no routine genetic analyses that are available to MBC patients at a high enough level of frequency that allows their physicians to very closely, and thus more adequately, monitor or predict changes in their tumors. The future aim of liquid biopsy is to develop it as a standard-of-care tool that can be used to help patients and their physicians monitor MBC more like a chronic illness that they can work together to manage in real time, as changes occur in their tumors.

Strategy/Rationale: Given the strength of our preliminary results, we would like to expand upon this study. Moving forward, we now aim to register future patients in a multi-year clinical trial to perform subsequent liquid biopsies and examine patients’ responses to therapies.

Through our study, women with advanced breast cancer will be offered a clinical liquid biopsy via a commercial vendor, and then we will draw blood at each subsequent progression for research testing. We will do purposeful sampling in order to include a solid representation of patients with various tumor subtypes.

Goal: This study will be a critical first step to analyze and better understand the clinical utility of, and stakeholder response to, cfDNA assessment in the care of women with MBC, thus giving rise to future additional studies for clinical validation.

Funding Request: \$75,000 (to help provide essential support for genetic sequencing, data analytics, and supplies)

Liquid Biopsies Budget			
	Number	Costs	Final Costs
Personnel - Research Scientist	0.5 FTE	50,000	\$25,000
Isolation of CTCs (RareCyte)	10	220	\$2,200
Whole genome amplification of DNA from CTCs, and sequencing	10	600	\$6,000
Streectubes (for cfDNA isolation from blood)	100	16	\$1,600
ddPCR Reagents			\$3,000
MammaSeq	110	300	\$33,000
Lab supplies			\$4,200

Total Budget			\$75,000
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Navigated care and research for women with metastatic breast cancer (MBC)

Navigation that ensures access to existing support services, symptom management, counseling, physical therapy, nutrition and personalized financial assistance has been vital for women with MBC served at Magee. The research navigator has been instrumental in engaging women in clinical trials as well as procuring samples for research.

We would like to continue the work of the MBC patient navigator and research navigator with the same level of GOH support, as these positions enhance and improve the patient experience in ways that may help improve patient outcomes.

Funding Request: \$35,000 (\$17,500 for each position)

Patient Services

Integrative Medicine Services

(Judy Herstine, Program Administrator, Women’s Cancer Services)

Background

Integrative Medicine Services works in conjunction with traditional medicine, to provide a more holistic approach to healing—mind, body and spirit—and benefit women diagnosed with breast cancer.

Acupuncture and massage services provided by the generosity of Glimmer has helped many women feel better by reducing the pain, stress and anxiety caused by cancer and its treatment.

Breast cancer robs our patients of their energy. By continuing to make these resources of acupuncture and accessible to our patients, we enhance their wellness and care for their emotional, spiritual and physical needs.

Funding Needs

We are requesting continuation of GOH’s support for these Integrative Medicine Services:

Acupuncture

Frances Desmone, Magee’s acupuncturist who holds a Masters of Acupuncture degree from the New England School of Acupuncture administers the sessions. The funds will be used to provide ten sessions of acupuncture for 60 breast cancer patients.

Massage

Massage therapy has helped our patients feel good as well as feel empowered in helping themselves cope with their unique challenges. Massage is a natural way to help relax and cope with stress, anxiety, headaches and pain, reducing the use of pharmacological treatment. In many cases, massage therapy can lift ones mood, improve sleep and enhance well-being.

Melody Nowak and her therapists at Melody’s Massage and Spa LLC provide hand and foot massages to our patients during their outpatient chemotherapy treatments. The service would occur a few days per week for a total of 6 hours each week.

Funding Request:

Activity	Unit Cost	Volume/Year	Total Annual Cost
Acupuncture (10 sessions)	\$640	40 patients/year	\$25,600
Massage by Melody’s Massage	\$75 per hour	312 hours/year	\$23,400

Summary of Requests

Research Requests	Cost
Liquid Biopsy	75,000
Metastatic Breast Cancer Patient and Research Navigator	35,000
Patient Services Requests	
Integrative Medicine: Acupuncture	25,600
Integrative Medicine: Massage	23,400
Total	\$159,000

**** Update on Research in Utilizing Liquid Biopsies ****

Through use of funds awarded by GOH in 2017, we have performed a retrospective analysis of all of the clinical liquid biopsy tests performed at UPMC over the last 2 years to understand the clinical decisions that physicians make when ordering a liquid biopsy. Of 230 tests, 128 (56%) were ordered by academic center providers (73 breast, 55 lung) and 102 (44%) from community providers (22 breast, 80 lung). 62 cases (31%) had results which included actionable mutations i.e. a clinical decision could be made. 28 (50%) resulted in a change in therapy while 28 (50%) did not. The finding of 230 tests leading to 28 cases where a change in therapy was made is in line with other studies. Ongoing studies will address whether more comprehensive testing will increase the rate of clinical adoption and changes in therapy.

The funds awarded by GOH in February 2017 (Check #1296 for \$26,600) focused on the clinical utility of the most common liquid biopsy test (Guardant360 - <http://www.guardanthealth.com/>). The abstract of that work was presented on December 7 at the San Antonio Breast Cancer Symposium, the largest breast cancer meeting. The results showed that ~95 tests were done and in ~25% a clinical decision was made upon the test. While results are in an early stage, physicians are starting to get more comfortable with the testing and results.

A copy of the abstract is provided below:

Title: Utilization of cell-free circulating tumor DNA for management of breast cancer: practices in academic and community oncology

Thomas RA, Klar N, Kiedrowski L, Nagy RJ, Lee AV, Brufsky A. University of Pittsburgh Medical Center, Pittsburgh, PA; Guardant Health, Redwood City, CA.

Background: Next-generation sequencing (NGS) of cell-free DNA (cfDNA) is increasingly being utilized to assess somatic genomic alterations in patients with breast cancer. We investigated the clinical use of such testing in breast cancer care in a major healthcare system with both academic and community-based practices. We also explored the observed genomic landscape in the analyzed patient cohort and whether treatment plans were modified based on the results.

Methods: A retrospective review of cfDNA NGS results (Guardant360) ordered at the University of Pittsburgh Medical Center for patients with breast cancer from 7/2015-3/2017 was performed. Test ordering patterns, the landscape of genomic alterations identified, and clinical use of select results were assessed.

Results: During this period 95 samples were submitted, 73 (77%) ordered by academic center providers and 22 (25%) from community providers. Alterations were detected in 88 samples (93%) with a median of 3 alterations per test. Five patients had serial samples ordered assessing dynamic cfDNA across clinical treatment and progressions, leaving 84 unique patients in the dataset. The average patient age was 57, and 95% of patients were female. Patients were most often observed to have alterations in *TP53* (51%), *PIK3CA* (44%), and *ESR1* (26%). Additional clinical data were collected for 48 patients with mutations or amplifications in *PIK3CA*, *ESR1*, and/or *ERBB2* (HER2) to assess for clinical use of genomic information.

Results were used to change clinical care in 13 (27%) of these cases. Community providers were more likely to use genomic results to guide clinical management in these cases (9/16, 56%) than academic providers (4/32, 12.5%), $p=0.001$. Of this patient subset, those with tests ordered by an academic provider had more lines of prior therapy at the time of testing vs. those in the community (average 5.9 vs 3.4 respectively, $p=0.019$).

Conclusions: CfDNA NGS analysis for somatic genomic alterations in breast cancer is being ordered clinically by both academic and community practices within this healthcare system. Results for a subset of clinically annotated patients were acted on more frequently by community-based ordering providers, which may be related to patients tested at academic sites having had more lines of prior treatment.

About Our Experts

Dr. Adrian Lee is Director, Women's Cancer Research Center, Magee-Womens Research Institute/University of Pittsburgh Cancer Institute; Director, Institute for Precision Medicine, UPMC/University of Pittsburgh; Professor, Department of Pharmacology and Chemical Biology.

Dr. Lee received B.Sc. and Ph.D. degrees in England, from the University of Kent in Canterbury, Kent (B.Sc.), and the University of Surrey, Guildford, Surrey (Ph.D.), and pursued his postdoctoral studies at the University of Texas Health Science Center in San Antonio, Texas. He was subsequently recruited to Baylor College of Medicine. In 2010, he was recruited to serve as Director, Women's Cancer Research Center the Magee-Womens Research Institute/University of Pittsburgh Cancer Institute, and also as Professor of Pharmacology & Chemical Biology, and Professor of Human Genetics at the University of Pittsburgh.

The goal of Dr. Lee's laboratory is to translate basic cell and molecular research findings into the understanding and treatment of breast cancer. This includes studies on the role of insulin-like growth factors in breast cancer, and identification of biomarkers for this targeted therapy. Dr. Lee has examined the effect of intratumor heterogeneity on prognostic tests in breast cancer, and is currently leading an effort to sequencing MBC to identify vulnerabilities for novel precision therapies.

Dr. Lee has published more than 120 peer reviewed research articles. His laboratory is also supported by funding from the Department of Defense, Susan G. Komen for the Cure, Breast Cancer Research Foundation, and other sources. Dr. Lee is on the Scientific Advisory Council for Susan G. Komen for the Cure. Dr. Lee serves on numerous national peer-review committees, and is on the Editorial Boards of several journals.

Additionally, as Director of the Institute of Precision Medicine (IPM) at UPMC/University of Pittsburgh, Dr. Lee's goal is to lead facilitation of the movement of precision medicine research into personalized clinical care. The IPM helps researchers and clinicians discover and exploit features about the risk of disease, the optimal treatment, the disease course, and the response to treatment. The four areas of focus at the IPM are: precision biobanking, genomics and proteomics, pharmacogenomics, and big data analytics.

Dr. Steffi Oesterreich is a Professor of Pharmacology and Chemical Biology at the University of Pittsburgh Cancer Institute, and Vice-Chair for Translational Pharmacology. She is also the Director of Education at the Women's Cancer Research Center, a collaboration between the Magee Women's Research Institute and UPMC Hillman Cancer Center. In addition, Dr. Oesterreich is a Graduate Faculty Member of the Interdisciplinary Biomedical Graduate Program in Molecular Pharmacology and in Molecular Pathology at the University of Pittsburgh School of Medicine. Dr. Oesterreich received her BS in Biochemistry at the Humboldt University, Berlin, Germany, in 1989. In 1992, she received her PhD in Molecular Medicine from the Humboldt University, Max-Delbrück Center for Molecular Medicine, Berlin, Germany. Post-graduation, she participated in a Fellowship in Breast Cancer at the University of Texas Health Science Center in San Antonio, Texas, and spent some time in Germany as an Alexander-von-Humboldt-Fellow.

Dr. Oesterreich received her PhD at the Humboldt-University in Berlin, Germany (1992). During this time, she performed research studies in the group of Professor Heinz Bielka at the Max Delbrück Centre for Molecular Medicine in Berlin-Buch, and became interested in breast cancer research. She conducted her postdoctoral studies in the laboratory of Dr. Suzanne Fuqua in the Division of Medical Oncology at the University of Texas Health Science Center in San Antonio, TX, headed by Dr. Kent Osborne (1992-1999). She then started her own group, and continued breast cancer research studies as Assistant and Associate Professor in the Lester and Sue Smith Breast Center at Baylor College of Medicine, Houston, TX. In 2010, she and her husband Dr. Adrian Lee were recruited to Pittsburgh.

Dr Oesterreich's laboratory focuses on resistance to hormonal therapies in patients with estrogen receptor-positive breast cancer, with a focus on metastatic disease, and invasive lobular breast cancer (ILC). Dr. Oesterreich enjoys to work in multi-disciplinary teams, and is committed to mentoring the next generation of breast cancer researchers.

She has authored over 140 scientific articles in the area of breast cancer, serves on editorial boards for Cancer Research and Hormones and Cancer, and functions as Associate Editor for Breast Cancer Research. Her research has continuously been funded by NCI, CDMRP, Susan G Komen, and BCRF for many years. Dr. Oesterreich is a Susan G Komen Scholar, thereby belonging to a selective group of leading national and international breast cancer experts. She recently finished chairing the Tumor Cell Biology Study Section at the NIH, and will be chairing the upcoming Gordon Research Conference on Hormones and Cancer.