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TITLE: Tumor Genomic Profiling in Breast Cancer Patients Using Targeted Massively Parallel Sequencing

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The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.
The overarching goal of this proposal is to use massively parallel sequencing to detect somatic genomic alterations in breast cancer tumor samples in order to identify genetic determinants of tumor behavior that may inform clinical decision-making. To date, we have developed a targeted sequencing platform that interrogates ~450 genes that are known to be altered in breast cancer and other cancers. We now plan to utilize this platform to study 150 tumor samples from women with ER+ breast cancer who have had early-, late- or no relapse following endocrine therapy. We have also begun to sequence tumor samples from patients with advanced breast cancer. To date, we have performed whole exome sequencing on 8 patients. In 4 patients, we identified somatic genomic alterations with potential clinical impact. In 5 of the 8 patients, we also obtained and sequenced tumor samples at the time of resistance to targeted therapies. In some cases, known mechanisms of resistance (i.e., ligand-binding domain mutations in ESR1) were identified. Analysis is currently underway to further elucidate causes of resistance in those cases where the mechanism is unclear.
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1. INTRODUCTION:

Knowledge of genetic changes that occur in cancer cells should ultimately facilitate individualized approaches to cancer treatment. However, methods to systematically profile cancers for relevant genetic changes in the clinical setting remain underdeveloped. The overarching goal of this proposal is to use cutting-edge genomic technology (massively parallel sequencing) in patients with breast cancer to identify genetic determinants of tumor behavior that may inform clinical decision-making. Two unmet clinical challenges in breast cancer motivate this approach. The first is the need for improved biological understanding of early stage estrogen-receptor positive (ER+) tumors with a high risk of recurrence. Systematic genetic profiling of early stage ER+ tumors may identify specific subsets of breast cancer and predict which patients are most likely to relapse. Second, there is a clear need for novel therapeutic strategies in metastatic breast cancers that have become resistant to standard therapies. Systematic genetic characterization of these resistant cancers might teach us about new therapeutic strategies or guide the development of targeted drug combinations that may help to overcome cancer drug resistance. Thus, in this study, we aim to profile a clinically annotated cohort of 150 ER+ breast tumors to look for genetic differences in both early-recurring and late-recurring tumors. In addition, we aim to prospectively profile 50 patients with advanced breast cancer in order to study the impact of our approach in a setting that may ultimately inform clinical decision-making.

2. KEYWORDS:
Breast Cancer
Estrogen Receptor
Resistance
Recurrence
Massively Parallel Sequencing
Next Generation Sequencing
Targeted Sequencing
Whole Exome Sequencing
Genomics
Personalized Medicine
Precision Medicine

3. OVERALL PROJECT SUMMARY:

AIM #1: To perform genomic profiling across a clinically annotated cohort of ER+ breast tumors

The goal of this Aim is to establish a breast-cancer focused mutation profiling platform and use it to study an annotated collection of tumor samples from patients with ER+ breast cancers. To date, we have completed the design and construction of this targeted sequencing platform that can be used on FFPE tumor samples. This platform targets all known breast cancer related genes identified in large sequencing studies of breast cancer samples from the past 2 years. We have also recently developed an updated version of this platform (v2.0), including several novel genomic alterations that we and others have recently identified in ER+ breast cancer samples. Sample collection and sequencing has been not yet started on this cohort due to unforeseen
technical issues with the implementation of the targeted sequencing platform. Now that the platform is operational, sequencing is expected to begin shortly.

**AIM 1A: To develop a breast cancer-focused massively parallel sequencing platform for FFPE samples**

4 large sequencing studies (published in *Nature* in 2012) used whole exome and/or whole genome sequencing to catalogue the landscape of genomic alterations in primary, treatment-naive breast cancers1-4. In total, 819 primary breast cancers were sequenced across these 4 studies, of which 529 were ER+ (Table 1). A fifth study by Matthew Ellis and colleague5 reported the sequencing of 77 pretreatment tumor biopsies (46 whole genomes and 31 whole exomes) from patients with luminal breast cancer treated with a neoadjuvant aromatase inhibitor. This study was designed to identify genomic biomarkers that may predict response or intrinsic (de novo) resistance to endocrine therapy. Based on Ki67 levels in the surgical specimens, samples were stratified into AI-sensitive (Ki67 < 10%, n = 48) and AI-resistant samples (Ki67 > 10%, n = 29). Mutations in MAP3K1 and possibly GATA3 were associated with AI-sensitivity, while TP53 mutations were associated with the AI-resistance. In the aggregate, these five studies have shed tremendous light onto the genomics of primary treatment-naive breast tumors.

As described in our original research proposal, we developed an enriched set of genes including these new significantly altered genes identified in breast cancer, as well as numerous other novel cancer genes that have recently been identified. In total, this design included all of the exons from 435 genes, selected introns to identify translocations from 22 genes, more extensive tiling across the entirety of 23 genes, and the promoter of the TERT gene. The resultant list of genomic coordinates were optimized and a set of baits were designed and synthesized. Implementation of the new baits into the targeted sequencing platform was delayed due to several unforeseen technical issues. However, these issues were resolved and we have recently completed testing and implementation of this platform, as described in our original research proposal.

More recently, we have identified several novel alterations in in ER+ breast tumors, including translocations in ESR1, the gene that encodes the estrogen receptor (Wagle, Garraway, and Arteaga, unpublished results). Given the potential importance of ESR translocations in ER+ breast cancer, we have further modified our bait design to include genomic coordinates across select introns in ESR1. In addition, two recent papers from the Broad Institute published in Nature in 2013 highlighted several novel cancer genes not previously identified as significant in cancer6,7. All of these alterations were also added to our targeted sequencing panel design, and a 2nd iteration (v2.0) is now under development. We expected to test this version over the next several months, and if successful it may replace v1.0.
TASKS:
- Design and optimization of breast-cancer specific platform (Month 1 – Month 4): COMPLETE

AIM 1B: To perform genomic profiling across a clinically annotated cohort of ER+ breast tumors
In this aim, we proposed to use our breast-cancer focused platform to profile a cohort of early stage ER+ breast tumors that have recurred after adjuvant therapy. Due to delays in the implementation of the sequencing platform outlined above, the collection and sequencing of these samples has not yet begun. Sample collection is now expected to be completed by month 15. However, due to significant process improvements and increased efficiency, the time for DNA extraction, library construction, hybrid selection, and targeted sequencing has been reduced since the time of grant application. Therefore, we now expect the entire cohort of 150 samples to have completed sequencing within 3 months total of sample collection (month 18). Analysis and validation will be completed by month 24, and statistical analysis should be completed by month 27, a total delay of 9 months.

TASKS (WITH REVISED TIMELINE):
- Sample collection (Month 12 – Month 15)
- DNA extraction, quantitation, and library construction (Month 16)
- Targeted massively parallel sequencing (Month 17 – Month 18)
- Analysis of sequencing data (Month 19 – Month 21)
- Validation of alterations (Month 21 – Month 24)
- Statistical analysis (Month 21 – Month 27)

REVISED MILESTONES:
- All samples collected by Month 15
- All sequencing completed by Month 18
- Statistical analysis completed by Month 24

AIM #2: To assess the feasibility of prospective sequencing in patients with advanced breast cancer
In this Aim, we proposed to apply our sequencing platform to patients with advanced breast cancer. The goal here is to study the feasibility of our approach in a setting that may ultimately inform clinical decision-making. This will serve as a proof-of-principle for how this platform could be used prospectively to uncover somatic genetic changes that impact the treatment and prognosis of patients with breast cancer. Because of the delay in implementing the new targeted sequencing platform, our focus here has been on performing whole exome sequencing in patients with advanced breast cancer.

We recently established a pipeline for prospective whole exome sequencing from FFPE tumor samples to support clinical decision making (and clinical trial enrollment) for appropriately consented patients with advanced cancers at the Dana-Farber Cancer Institute (DFCI) known as CanSeq. We conducted a pilot study on 16 patients that has enabled optimization of various aspects of our emerging clinical sequencing pipeline, including sample acquisition, DNA
extraction, sequencing, and analysis. The somatic and germline alterations were analyzed using a newly-developed heuristic algorithm that we presented at the 2012 ASCO Annual Meeting (Van Allen, Wagle, et al). This algorithm applies a categorization framework that incorporates the degree of actionability and level of evidence for that action. A similar algorithm has also been developed for germline alterations. We have also developed a customized report that streamlines the results of these algorithms for presentation to our Cancer Genomics Evaluation Committee, a multi-disciplinary “genomics tumor board” which makes decisions about the interpretation and clinical actionability of somatic and germline alterations. Somatic analysis of the first 16 patients demonstrated at least one plausibly actionable somatic alteration linked to an approved or experimental therapy in 15 out of 16 cases. This work was presented in two posters at the 2013 AACR Annual Meeting (Wagle N, Van Allen E, et al, 2013 AACR Annual Meeting; Van Allen EM, Wagle N, et al., 2013 AACR Annual Meeting). Our manuscript describing this approach and the pilot study is currently in press in Nature Medicine (Van Allen, Wagle, et al, 2014).

AIM 2A: To assess the clinical impact of prospective genomic profiling in advanced breast cancer

Using this CanSeq pipeline, we have begun to sequencing patients with advanced breast cancer in order to identify genomic alterations that may aid with clinical decision making. To date, we have performed whole-exome sequencing on tumor samples from 8 patients with advanced breast cancer. The relevant genomic findings are summarized in Table 2:

<table>
<thead>
<tr>
<th>Patient</th>
<th>Clinically Relevant Somatic Alterations Identified</th>
<th>Associated Clinical Actions</th>
<th>Clinical Actions Taken Due to Sequencing Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>PIK3CA activating mutation</td>
<td>PI3-kinase inhibitor</td>
<td>None (patient is deceased)</td>
</tr>
<tr>
<td>Patient 2</td>
<td>CDKN1B loss-of-function mutation</td>
<td>CDK inhibitor</td>
<td>CDK4/6 inhibitor trial enrollment</td>
</tr>
<tr>
<td>Patient 3</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 4</td>
<td>FGFR1 amplification</td>
<td>FGFR inhibitor</td>
<td>None to date</td>
</tr>
<tr>
<td>Patient 5</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 6</td>
<td>JAK2 mutation</td>
<td>JAK2 inhibitor</td>
<td>None to date</td>
</tr>
<tr>
<td>Patient 7</td>
<td>PIK3CA activating mutation</td>
<td>PI3-kinase inhibitor</td>
<td>PI3-kinase inhibitor trial (mutation was already known)</td>
</tr>
<tr>
<td>Patient 8</td>
<td>&lt;in analysis&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 2**

Enrollment, sequencing, analysis, interpretation, and reporting to physicians and patients continue. An interim analysis of feasibility and clinical impact is planned when enrollment reaches 10 patients, as described in the original proposal.

**TASKS:**
- Protocol activation (Month 1 – Month 3): **COMPLETE**
- Patient enrollment (Month 4 – Month 36): **IN PROGRESS**
• Sample acquisition (Month 4 – Month 36):  
  **IN PROGRESS**
• Genomic profiling (including DNA extraction, library construction, sequencing, and validation) (Month 4 – Month 36):  
  **IN PROGRESS**
• Interpretation of genomic alterations and reporting to physicians/patients (Month 4 – Month 36):  
  **IN PROGRESS**
• Analysis of feasibility and clinical impact (Month 4 – Month 36):  
  **IN PROGRESS**

**MILESTONES:**
• Protocol activated and patient enrollment begins by **Month 4:**  
  **COMPLETE**
• Sequencing of first 5-10 patients completed and reported to physician/patient by **Month 9:**  
  **8 PATIENTS COMPLETE**
• Analysis of feasibility and clinical impact of first 5-10 patients by **Month 12:**  
  **IN PROGRESS**
• Sequencing of first 20 patients completed and reported to physician/patient by **Month 18**
• Analysis of feasibility and clinical impact of first 20 patients by **Month 21**
• Sequencing of at least 50 patients completed and reported to physician/patient by **Month 33**
• Analysis of feasibility and clinical impact of 50 patients by **Month 36**

**AIM 2B: To use whole-exome sequencing to identify genomic mechanisms of therapeutic resistance**
The goal of this aim is perform whole exome sequencing in breast cancer patients who develop resistance to targeted therapies (e.g., endocrine therapies, anti-Her2 therapies, PI3K inhibitors, mTOR inhibitors) in order to identify novel resistance mechanisms. These patients will be re-consented for repeat metastatic biopsy and the new samples profiled to determine alterations that may have led to therapeutic resistance.

Of the 8 enrolled patients described above, 5 patients were profiled at the time of resistance to a targeted therapy, as shown in **Table 3:**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Agent to Acquired</th>
<th>Which Resistance Was Acquired</th>
<th>Candidate Identified in Resistance Mutation Tumor</th>
<th>Detectable in Pretreatment Tumor?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Endocrine Therapy</td>
<td>ESR1 resistance mutation</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Patient 2</td>
<td>Endocrine Therapy</td>
<td>ESR1 resistance mutation</td>
<td>Sample Unavailable</td>
<td></td>
</tr>
<tr>
<td>Patient 3</td>
<td>Endocrine Therapy</td>
<td>ESR1 resistance mutation</td>
<td>&lt;SAMPLE PENDING&gt;</td>
<td></td>
</tr>
<tr>
<td>Patient 6</td>
<td>MET Inhibitor</td>
<td>Unknown at present</td>
<td>&lt;SAMPLE PENDING&gt;</td>
<td></td>
</tr>
<tr>
<td>Patient 7</td>
<td>PI3Kalpha inhibitor</td>
<td>Unknown at present</td>
<td>Unknown at present</td>
<td></td>
</tr>
</tbody>
</table>
Table 3

We are in the process of obtaining and sequencing the pretreatment samples from several of these patients, as indicated. A comparative analysis of the paired pre-treatment and post-resistance samples will continue as we obtain additional samples. We will continue to obtain pre-treatment and resistant samples from additional patients as they become available.

Tasks:

- Whole exome sequencing of patients with acquired resistance to targeted therapies (Month 9 – Month 36): IN PROGRESS

Milestones:

- Whole exome sequencing on first 3-6 patients with acquired resistance completed by Month 16: 3 PATIENTS COMPLETE
- Whole exome sequencing of at least 15 patients with acquired resistance completed by Month 33

4. Key Research Accomplishments:

- Development of a novel targeted sequencing platform that includes ~450 genes (v1.0) that are significantly altered in breast cancer and other cancers, including novel unpublished alterations that we have recently identified in ER+ breast cancers
- Development of a prospective whole exome sequencing pipeline (CanSeq) that includes sequencing from FFPE samples, analysis, curation, and interpretation of clinically relevant somatic and germline alterations, discussion of key findings by the Cancer Genome Evaluation Committee, and return of results to physicians and patient (Van Allen, Wagle, et al, Nature Medicine, In Press)

5. Conclusion:

To date, we have made significant progress on this research project. Given the progress to date, we anticipate that we will achieve our stated research goals by the end of the grant term. To accomplish this, we will utilize the targeted sequencing panel we have developed to profile 150 early stage ER+ breast cancers, as we have described. We will continue to perform whole exome and targeted sequencing on patients with advanced breast cancer until we reach our stated goal of 50 patients. For the subset of patients who develop resistance to therapies, we will perform additional sequencing to compare their resistant tumor to their pre-treatment sensitive tumor, as we have demonstrated for several patients already.

Once successfully completed, this work should provide new knowledge that informs the development of novel treatment strategies in breast cancer. These include treatments that may prevent early and/or late recurrence in ER+ breast cancers, new approaches to determining how best to use targeted therapies in advanced breast cancer, and novel strategies to overcome resistance mechanisms. If widely deployed, implementation of this approach may open new opportunities to link cancer genomics with molecular features, clinical outcomes, and
treatment response in patients with breast cancer. This approach may ultimately impact clinical practice by offering a categorical means to identify genetic changes affecting genes and pathways targeted by existing and emerging drugs, thereby speeding the advent of personalized cancer medicine.

6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

a. Manuscripts:

(1) Lay Press:

None

(2) Peer-Reviewed Scientific Journals:


8. Van Allen EM*, Wagle N*, Sucker A, Treacy D, Johannessen C, Goetz EM, Place CS,

(*Dual-First Author)


(*Dual-First Author)


(3) Invited Articles:


(4) Abstracts:


(*Dual-First Author)

b. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.

**FORMAL TEACHING OF PEERS**

2013  “Genomic Profiling in Breast Cancer”  Lecture
Breast Cancer: New Horizons, Current Controversies
Dana-Farber Cancer Institute / Harvard Medical School

**LOCAL INVITED PRESENTATIONS**

2013  “Tumor Genomic Profiling and Personalized Cancer Medicine” (Part I)  Lecture
DF/HCC Clinical Investigator Course

2013  “Tumor Genomic Profiling and Personalized Cancer Medicine” (Part II)  Lecture
DF/HCC Clinical Investigator Course

2013  “Implementing Genomics-Driven Cancer Medicine: The Genomics Superhighway Meets the Bikepath of Medical Practice” (with Atul Gawande, MD)  Invited Talk
Cancer Program Meeting, Broad Institute

2013  “Clinical and Translational Cancer Genomics”  Invited Talk
Scientific Speaker Series
Genomics Platform, Broad Institute

2013  “Clinical and Translational Cancer Genomics”  Seminar
Breast Oncology Seminar Series
Dana-Farber Cancer Institute

2013  “Clinical Cancer Genomics and Precision Cancer Medicine”  Seminar
Radiation Oncology Conference
BWH/Dana-Farber Cancer Institute

2013  “Clinical Sequencing and Precision Cancer Medicine”  Seminar
Massachusetts General Hospital Cancer Center

2013  “Clinical Cancer Genomics and Precision Cancer Medicine”  Seminar
Thoracic Oncology Program Seminar Series
Dana-Farber Cancer Institute

2013  “Clinical Sequencing and Precision Cancer Medicine”  Invited Talk
Cancer Program Meeting, Broad Institute

**National**

2013  “CanSeq: The Use of Whole Exome Sequencing To Guide the Care of Cancer Patients”  Invited Talk
62nd Meeting of the National Cancer Institute
Director’s Consumer Liaison Group (DCLG)
National Cancer Institute
7. INVENTIONS, PATENTS AND LICENSES:

Nothing to report.

8. REPORTABLE OUTCOMES:
Nothing to report.

9. OTHER ACHIEVEMENTS:

a) I became the Co-Chair of the NHGRI Clinical Sequencing Exploratory Research Consortium’s Sequencing Standards Working Group, a working group focused on the development of standards for clinical sequencing. The working group consists of members from 9 U.S. institutions conducting clinical sequencing research funded by the NHGRI.

b) I obtained several awards and grants, several of which are related to the preliminary data generated by this award (indicated with an *):

2012 – 2014  *Tumor and Germline Whole Exome Sequencing in Young Women with Breast Cancer*
Susan F. Smith Ctr for Women’s Cancers Executive Council: Molecular Signatures of Human Cancers (Wagle)
Principal Investigator ($144,000)
The overarching goal of this project is to improve our understanding of breast cancer in young women by using cutting-edge genomic technology (massively parallel, or “next-generation” sequencing) to comprehensively characterize all of the known genes (the whole exome) from a collection of tumor and blood samples from 100 women who developed breast cancer before the age of 35.

*2013 – 2015 Systematic genomic profiling of endocrine-resistant breast cancer*
Landon Foundation-AACR INNOVATOR Award for Research in Personalized Cancer Medicine (Wagle)
Principal Investigator ($100,000)
The overarching goal of this research is to use comprehensive genomic profiling to test the hypothesis that somatic genetic differences may contribute to endocrine-resistance in breast cancer. Toward this end, a major focus of this grant will leverage massively parallel sequencing technology to characterize the whole exome (the protein coding sequence of the genome) and whole transcriptome (all mRNA transcripts in the cell) of prospectively collected breast cancer samples from women with acquired resistance to hormonal therapies.

2013 – 2018  *Overcoming Resistance to HER2-Directed Therapies for Breast Cancer, Dana-Farber/Harvard SPORE in Breast Cancer (Project 2)*
The National Cancer Institute / National Institutes of Health 1P50CA168504-01A1 (Winer)
Co-Investigator
This project uses state-of-the-art genetically engineered mouse models and a cutting edge clinical trial to evaluate resistance mechanisms in HER2+ breast cancer. It seeks to overcome this resistance by further interrogating the PI3 kinase pathway, and will evaluate sensitivity and resistance to PI3 kinase inhibitors.

2013 – 2018  *Tissue and Pathology Core, Dana-Farber/Harvard SPORE in Breast Cancer (Core D)*
The National Cancer Institute / National Institutes of Health 1P50CA168504-01A1 (Winer)
Co-Director
The Tissue and Pathology Core will maintain tissue/blood repositories for the SPORE Projects.
This Core will also provide pathology services that are critical to many of the translational research aims in the Projects.

2014 – 2015 Exceptional Responses in Cancer
Next Generation Fund of the Broad Institute of Harvard and MIT (Wagle)
Principal Investigator ($100,000)
This project uses deep molecular characterization, including whole exome and whole transcriptome sequencing, of tumors from patients who have had exceptional responses – exquisite sensitivity or unexpectedly durable responses to treatment – in order to better understand predictors of response and to develop novel strategies for treating cancer.

*2014 – 2016 Identifying resistance mechanisms in ER+ breast cancer by translational genomics
Dana-Farber/Harvard SPORE in Breast Cancer Career Development Award (Wagle)
Principal Investigator ($80,000)
The goal of this research is to apply both genomic characterization and systematic functional approaches to test the hypothesis that somatic genetic differences may contribute to endocrine-resistance in breast cancer. To accomplish this, we will employ complementary genomic and in vitro experimental approaches that address two critical challenges facing clinicians who treat ER+ breast cancer: identifying determinants of resistance to endocrine therapy, and elucidating the spectrum of clinically relevant alterations and actionable dependencies in patients with endocrine-resistant breast cancer.

10. TRAINING AND PROFESSIONAL DEVELOPMENT:
My training has been enhanced by a number of ongoing weekly meetings and working groups that focus on areas in which I seek to continue my development. These include weekly laboratory meetings, a Cancer Resistance working group (monthly), a Cancer Genome Working group (weekly), a weekly Cancer Program Meeting, the Breast Oncology tumor board (weekly) and the Breast Oncology weekly seminar series, as well as a number of other periodic conferences and seminar series. I have had the opportunity to attend these seminars and courses as well as present my work in them. In addition, I have had the opportunity to attend numerous scientific meetings over the past year, including the San Antonio Breast Cancer Symposium, the AACR Annual Meeting, the ASCO Annual Meeting, the AACR-EORTC-NCI Meeting on Molecular Targets and Cancer Therapeutics, and several meetings and workshops of the NHGRI Clinical Sequencing Exploratory Research Consortium.

11. REFERENCES:

