

AWARD NUMBER: W81XWH-17-1-0595

TITLE: Dynamic Response of Disseminated Tumor Cells and Circulating  
Tumor Markers to Targeted Adjuvant Therapy

PRINCIPAL INVESTIGATORS: Angela DeMichele

CONTRACTING ORGANIZATION: **The Trustees of the University of Pennsylvania  
Philadelphia, PA 19104**

REPORT DATE: October 2018

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command  
Fort Detrick, Maryland 21702-5012

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# REPORT DOCUMENTATION PAGE

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|   |                    |                     |                                   |                            |  |  |
|---|--------------------|---------------------|-----------------------------------|----------------------------|--|--|
| <b>1. REPORT DATE</b><br>October 2018   |                    |                     | <b>2. REPORT TYPE</b><br>Annual   |                            | <b>3. DATES COVERED</b><br>30 Sep 2017 - 29 Sep 2018 |  |
| <b>4. TITLE AND SUBTITLE</b><br><br>Dynamic Response of Disseminated Tumor Cells and Circulating Tumor Markers to Targeted Adjuvant Therapy   |                    |                     |                                   |                            | <b>5a. CONTRACT NUMBER</b>                           |  |
|   |                    |                     |                                   |                            | <b>5b. GRANT NUMBER: W81XWH-17-1-0595</b>            |  |
|   |                    |                     |                                   |                            | <b>5c. PROGRAM ELEMENT NUMBER</b>                    |  |
| <b>6. AUTHOR(S)</b><br>Lewis A. Chodosh, MD, PhD<br>Angela DeMichele, MD, MSCE<br><br>E-Mail:   |                    |                     |                                   |                            | <b>5d. PROJECT NUMBER</b>                            |  |
|   |                    |                     |                                   |                            | <b>5e. TASK NUMBER</b>                               |  |
|   |                    |                     |                                   |                            | <b>5f. WORK UNIT NUMBER</b>                          |  |
| <b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</b><br><br>The Trustees of the<br>University of Pennsylvania<br>3451 Walnut Street, Franklin<br>Building, 5th Floor<br>Philadelphia, PA 19104   |                    |                     |                                   |                            | <b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>      |  |
| <b>9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b><br><br>U.S. Army Medical Research and Materiel Command<br>Fort Detrick, Maryland 21702-5012  |                    |                     |                                   |                            | <b>10. SPONSOR/MONITOR'S ACRONYM(S)</b>              |  |
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| <b>12. DISTRIBUTION / AVAILABILITY STATEMENT</b><br><br>Approved for Public Release; Distribution Unlimited   |                    |                     |                                   |                            |  |  |
| <b>13. SUPPLEMENTARY NOTES</b>  |                    |                     |                                   |                            |  |  |
| <b>14. ABSTRACT</b><br>A significant proportion of patients who receive adjuvant therapy for breast cancer recur, usually with distant metastatic disease. Since recurrent breast cancer is typically incurable, the propensity of breast cancers to recur following treatment is the most important determinant of clinical outcome. Breast cancer recurrences arise from the pool of local and disseminated residual tumor cells (DTCs) that survive in their host in a presumed dormant state following treatment of the primary breast cancer. Consistent with this, DTCs present in the bone marrow, and circulating tumor cells (CTCs) present in the bloodstream, after treatment are strongly associated with an increased risk of recurrence. At present, however, the underlying biology that enables residual tumor cells to remain dormant, often for years, evade therapy and ultimately recur is poorly understood. Moreover, the molecular properties of DTCs and CTCs, as well as their biological relationship and comparative utility for evaluating risk and response to therapy are as yet undefined. This lack of understanding, along with the lack of therapeutic approaches specifically targeting these cells as a means to prevent recurrence, constitute major obstacles to the successful treatment of breast cancer patients. Our findings to date advance new approaches for detecting and characterizing minimal residual disease. |                    |                     |                                   |                            |  |  |
| <b>15. SUBJECT TERMS</b><br>Minimal residual disease, disseminated tumor cells, circulating tumor cells, cell-free tumor DNA, mouse models  |                    |                     |                                   |                            |  |  |
| <b>16. SECURITY CLASSIFICATION OF:</b>  |                    |                     | <b>17. LIMITATION OF ABSTRACT</b> | <b>18. NUMBER OF PAGES</b> | <b>19a. NAME OF RESPONSIBLE PERSON</b><br>USAMRMC    |  |
| <b>a. REPORT</b>  | <b>b. ABSTRACT</b> | <b>c. THIS PAGE</b> |                                   |                            | <b>19b. TELEPHONE NUMBER</b> (include area code)     |  |
| Unclassified  | Unclassified       | Unclassified        | Unclassified                      |                            |  |  |

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## 1. INTRODUCTION:

The goal of this proposal is to delineate the dynamic changes in abundance, proliferative state, and molecular properties of different RTC subsets that occur during tumor progression, and in response to adjuvant therapies. This will enable elucidation of the biological and genomic relationship of RTC subsets, the concordance of changes in cellular and molecular markers for MRD that resides in different anatomic compartments and the identification of circulating tumor markers (CTM) that accurately identify the presence of DTC<sub>bm</sub> and extent of residual tumor burden. In doing so, the proposed studies will advance understanding of the biological properties of dormant RTCs that enable their survival which, in turn, is essential for understanding the mechanisms by which these cells escape therapy, persist in a dormant state, and ultimately give rise to recurrent, incurable breast cancers.

2. **KEYWORDS:** Minimal residual disease, disseminated tumor cells, circulating tumor cells, cell-free tumor DNA, mouse models, tumor recurrence
3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction*

### o What were the major goals of the project?

Aim 1 is designed to define the dynamic changes in disseminated tumor cells (DTCs) and circulating tumor markers that occur during tumor dormancy and recurrence in a genetically engineered mouse model for dormant minimal residual disease and recurrence.

Aim 2 is designed to define the dynamic changes in disseminated tumor cells (DTCs) and circulating tumor markers that occur following adjuvant therapy in a genetically engineered mouse model for dormant minimal residual disease and recurrence.

Aim 3 is designed to compare the dynamic response of circulating tumor markers and bone marrow DTCs to targeted adjuvant therapy in breast cancer patients. This requires the identification of a population of high-risk breast cancer survivors in whom we can identify these markers for translational studies that extend the work from mouse to patients.

### o What was accomplished under these goals?

**Aim 1 (Chodosh):** In order to accomplish this aim, and in accordance with the approved Statement of Work, we performed the following work during the initial reporting period:

- o Major Task 1: Perform and analyze residual tumor cell enumeration studies during tumor progression. This task has been initiated and proceeds on schedule as outlined in the approved SOW.
  - Subtask 1.1 (Chodosh): Transgenic breeding colonies were established to produce female primary tumor donor mice of the desired genotype. *MMTV-rtTA;TetO-HER2* and *MMTV-rtTA;TetO-HER2;TetO-TurboCre;Rosa26-lox-stop-lox-YFP* mice were generated. In addition, *TetO-H2B-mCherry* mice were backcrossed onto an FVB background to facilitate future experiments using mice incorporating this fluorescent reporter into their genomes.
  - Subtask 1.2 (Chodosh): At 6 weeks of age, oncogene expression was induced in donor mice of appropriate genotypes from Subtask 1.1 by administering doxycycline. Donors were monitored by palpation for the development of invasive mammary adenocarcinomas and for tumor growth. Sixteen *MMTV-rtTA;TetO-HER2* tumors primary tumors were digested to single cell suspensions and frozen for future use.
  - Subtask 1.3 (Chodosh): To identify suitable primary tumors for the experiments proposed, orthotopic tumor assays were performed using fluorescently-marked primary tumors from 6 donor

mice produced in Subtask 1.2. Single cell suspensions from primary tumors that had been digested enzymatically were used to generate orthotopic primary tumors in NCr *nu:nu* recipient mice. Orthotopic primary tumors were monitored until they reached the maximum size allowable by IACUC guidelines to maximize the likelihood that micrometastatic tumor cells would be present in bone marrow (BM) and lung. Primary tumors, blood, bone marrow and lung tissues were harvested from all orthotopic tumor-bearing mice. Ongoing analysis of bone marrow for DTCs has thus far revealed that a majority of mice bearing orthotopic tumors harbor detectable DTCs. Ongoing analysis of blood for CTCs has thus far revealed that approximately one-third of mice harbor detectable CTCs.

- Major Task 2 (Chodosh): Perform and analyze ptDNA quantification studies during tumor progression. This task has been initiated and proceeds on schedule as outlined in the approved SOW.
  - cfDNA and ptDNA levels were quantified in blood harvested from euthanized tumor-bearing mice. Blood samples harvested both from the submandibular vein and by cardiac puncture were assayed. Initial findings confirm that cfDNA and ptDNA are present, detectable, and quantifiable by droplet digital PCR in nearly all tumor-bearing mice. Data obtained during the initial reporting period also indicate that ptDNA represents approximately 5-15% of cfDNA present. However, initial data suggest that the correlation between ptDNA levels in blood from the submandibular vein and ptDNA levels in cardiac blood is relatively low.
- Major Task 3 (Chodosh): Perform and analyze WES, RNA-Seq and WGS studies on isolated cell populations. This task has been initiated and proceeds on schedule as outlined in the approved SOW.
  - To enable these studies, during the initial reporting period we performed whole exome sequencing (WES), RNA-Seq, and shallow whole genome sequencing (sWGS) on single breast cancer cells isolated by fluorescence activated cell sorting or by DEPArray to determine the feasibility of single cell genome analysis, and to compare and optimize whole transcriptome amplification methods, whole genome amplification methods, whole exome sequencing platform, whole genome sequencing platform, and RNA-Seq platform. These analyses are currently underway, but indicate success in amplifying RNA and DNA from single isolated cancer cells.

**Aim 2 (Chodosh):** In order to accomplish this aim, and in accordance with the approved Statement of Work, we performed the following work during the initial reporting period:

- Major Task 4 (Chodosh): Perform adjuvant therapy studies with hydroxychloroquine (HCQ) and everolimus (EVE) on mice bearing residual disease. This task has been initiated and proceeds on schedule as outlined in the approved SOW.
  - Subtask 4.1 Using approaches analogous to those described in subtask 1.3. primary tumor cells from a HER2-induced tumor were orthotopically injected into the mammary glands of NCr *nu:nu* mice maintained on doxycycline. Following primary tumor outgrowth, mice were then assigned to treatment groups vehicle control, hydroxychloroquine (HCQ), everolimus (EVE), and HCQ+EVE. Mice were treated beginning at 21 days following doxycycline withdrawal and the initiation of tumor regression, which corresponds to roughly one week following the onset of tumor dormancy in mice bearing minimal residual disease. Mice are currently being monitored for the incidence and latency of tumor recurrence. Subsets of mice are being sacrificed at stages corresponding to primary tumor and following increasing periods of treatment. At the time of sacrifice, mammary gland and lung, bone marrow, and blood are being harvested, processed and stored for future analysis.
- Major Task 5 (Chodosh): Perform and analyze residual tumor cell enumeration studies in mice in response to adjuvant therapy. This task has been initiated and proceeds on schedule as outlined in the approved SOW.
  - cfDNA is being prepared from blood samples obtained from mice euthanized from adjuvant therapy studies with HCQ and EVE, as outlined in Major Task 4. Buffy coat isolated from blood samples have been used to prepare cytopsin slides for assessment of CTCs. Bone marrow samples

from mice euthanized from adjuvant therapy studies with HCQ and EVE, as outlined in Major Task 4, have been used to prepare cytospin slides for assessment of DTCs.

**Aim 3:** In order to accomplish this aim, and in accordance with the approved Statement of Work, we performed the following work during the initial reporting period:

- Major Task 6 (Chodosh/DeMichele): Compare the dynamic response of circulating tumor markers and bone marrow DTCs to targeted adjuvant therapy in breast cancer patients. This task has been initiated and proceeds on schedule as outlined in the approved SOW.
  - Subtask 6.1 (DeMichele): We have modified the SURMOUNT/CLEVER protocols to enable expanded blood collection and bone marrow collections. The CLEVER amendment includes language regarding the DOD study funding and changes to the protocol.
  - Subtask 6.2 (DeMichele): All necessary documentation has been submitted to the DOD HRPO office for this approval. A HRPO Approval Memorandum for A-20384 and A-20385 (Proposal Log Numbers BC161729 and BC161729P1, Award Numbers W81XWH-17-1-0594 and W81XWH-17-1-0595) was received on April 12, 2019.
  - Subtask 6.3 (DeMichele): For this task, we have implemented a cohort study entitled “Penn SURMOUNT” and companion clinical trial entitled “CLEVER” to identify breast cancer survivors who harbor DTCs and offer them targeted interventions. Patients eligible for the SURMOUNT screening study must meet the following eligibility requirements: 1) diagnosed within past 5 years, 2) High risk primary breast cancer defined as having at least one of the following: a) node positive disease; b) triple negative (ER-/PR-/Her2-) disease; c) ER+ disease with an Oncotype Recurrence Score of  $\geq 25$ ; or d) residual disease after neoadjuvant therapy. Patients who present to the Rowan Breast Center at the University of Pennsylvania, undergo clinical screening eligibility assessment to rule out the presence of metastatic disease, and have blood and bone marrow obtained for study. We have enrolled 122 patients on the PENN-SURMOUNT study as of January 2019. These patients have generated 116 blood specimens and 117 bone marrow aspirate specimens for study. Of these, 35 patients had bone marrow aspirates that are DTC positive, and are in process or enrolled on CLEVER trial, and are having samples collected for Aim 3. Efforts are continuously underway to obtain primary tumor tissue from these patients for the planned analyses. Bone marrow aspirate and blood samples are processed for assessment of the Aim 3 tasks in the laboratory of Dr. Chodosh.
  - Subtask 6.4 (Chodosh/DeMichele): Drs. Chodosh and DeMichele have maintained regular contact with the consumer advocate team. Our full consumer advocate board meets quarterly to review our progress and as needed for new issues that arise.
  - Subtask 6.5 (Chodosh/DeMichele): The study team holds regular meetings every 2 weeks to review the conduct of the studies. A DSMB (which includes a consumer advocate) reviews enrollment and safety data quarterly.
- Major Task 7 (Chodosh/DeMichele): Perform and analyze residual tumor cell enumeration studies in enrolled CLEVER patients. This task has been initiated and proceeds on schedule as outlined in the approved SOW. Patient bone marrow samples are being evaluated using both the DTC-IHC and DTC-Flow assays. Results are reviewed on an ongoing basis.
- Major Task 8 (Chodosh/DeMichele): Perform and analyze ptDNA quantification studies in enrolled CLEVER patients. This task has been initiated and proceeds on schedule as outlined in the approved SOW. Plasma from CLEVER patient blood samples is being harvested, frozen and stored on an ongoing basis. Since evaluating ptDNA requires the identification of a clonal mutation present in the patient’s primary tumor, during the initial reporting period we have focused on evaluating whole exome sequencing testing platforms that can be performed from DNA extracted from formalin fixed paraffin-embedded primary tumor samples. Evaluation of resulting sequencing data are underway.
- **What opportunities for training and professional development has the project provided?**

- Nothing to report. This portion of the award did not include any training component.
- **How were the results disseminated to communities of interest?**
    - Given that accrual is ongoing, we have not yet had any data appropriate to report. However, we have presented the study design in a number of venues, including the San Antonio Breast Cancer Symposium (December 2018), the Translational Breast Cancer Research Consortium (November 2018), The Metastatic Breast Cancer Conference (Johns Hopkins University, November 2018) and through numerous Grand Rounds (for example MGH September 2018) to raise awareness of the studies to colleagues and patients. This has resulted in numerous referrals from medical oncologists from other institutions. To date, patients from approximately 15 states have travelled to the University of Pennsylvania to participate in these studies.
  - **What do you plan to do during the next reporting period to accomplish the goals?**
    - We will continue to enroll to these studies to meet our accrual goal of 60 DTC+ patients on the CLEVER Trial. We will continue quality checks on the specimens that have been obtained, including assessment of test/retest reliability for the DTC assessment and QA of tissues from primary tumors that are obtained. We will continue follow up of DTC+ patients.

4. **IMPACT:**

- **What was the impact on the development of the principal discipline(s) of the project?**
  - These studies have contributed to the awareness of minimal residual disease as a significant clinical problem and target for intervention in breast cancer. The studies that were started as part of this initiative have led to 2 additional clinical intervention trials for patients who are DTC+: The GLACIER trial (funded by the Breast Cancer Research Consortium/Pfizer) and the ABBY trial (funded by Lilly). These studies have also led to new research collaborations with Menarini/Silicon Biosystems and EPIC Biosciences (for CTC studies) and with Natera and SafeSeq (for circulating tumor cfDNA studies).
- **What was the impact on other disciplines?**
  - Nothing to report on this portion of the project.
- **What was the impact on technology transfer?**
  - Nothing to report on this portion of the project
- **What was the impact on society beyond science and technology?**
  - Nothing yet to report as the study is ongoing.

5. **CHANGES/PROBLEMS:** *The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

- **Changes in approach and reasons for change**
  - Nothing to report. No significant changes in the approach have been made

- **Actual or anticipated problems or delays and actions or plans to resolve them**
  - Nothing to report.
- **Changes that had a significant impact on expenditures**
  - Nothing to report.
- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
- **Significant changes in use or care of human subjects**
  - No changes in use or care of human subjects has occurred. Quarterly safety assessments are carried out as part of the CLEVER protocol. These are reviewed by the CLEVER DSMB and Medical Monitor. There are early stopping rules associated with significant toxicity. As of the January 2019 review, there have been no new safety signals and the DSMB has allowed the study to proceed without interruption.
- **Significant changes in use or care of vertebrate animals.**
  - Nothing to report.
- **Significant changes in use of biohazards and/or select agents.**
  - Nothing to report.

**6. PRODUCTS:**

- **Publications, conference papers, and presentations**
  - Nothing to report.
- **Website(s) or other Internet site(s)**
  - Nothing to report
- **Technologies or techniques**
  - Nothing to report
- **Inventions, patent applications, and/or licenses**
  - Nothing to report
- **Other Products**
  - Nothing to report

**7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

- **What individuals have worked on the project?**

|               |               |
|---------------|---------------|
| Name:         | Lewis Chodosh |
| Project Role: | PI            |

|  |                              |
|--|------------------------------|
| Researcher Identifier (e.g. ORCID ID): |                              |
| Nearest person month worked:           | 1                            |
| Contribution to Project:               | Project direction            |
| Funding Support:                       | NIH, V-Foundation, BCRF, DOD |

|  |                              |
|--|------------------------------|
| Name:                                  | Angela DeMichele             |
| Project Role:                          | Partnering PI                |
| Researcher Identifier (e.g. ORCID ID): |                              |
| Nearest person month worked:           | 1                            |
| Contribution to Project:               | Project direction            |
| Funding Support:                       | NIH, V-Foundation, BCRF, DOD |

|  |  |
|--|--|
| Name:                                  | Lauren Bayne   |
| Project Role:                          | Clinical Research Coordinator  |
| Researcher Identifier (e.g. ORCID ID): |  |
| Nearest person month worked:           | 5  |
| Contribution to Project:               | Patient sample acquisition for CTC and ptDNA analysis, clinical data abstraction and handling. |
| Funding Support:                       | NIH, V-Foundation, BCRF, DOD   |

|  |                                       |
|--|---------------------------------------|
| Name:                                  | George Belka                          |
| Project Role:                          | Project Director                      |
| Researcher Identifier (e.g. ORCID ID): |                                       |
| Nearest person month worked:           | 1                                     |
| Contribution to Project:               | Project management, sample processing |
| Funding Support:                       | NIH, BCRF, DOD                        |

|  |                        |
|--|------------------------|
| Name:                                  | Julie Castro           |
| Project Role:                          | Research Specialist    |
| Researcher Identifier (e.g. ORCID ID): |                        |
| Nearest person month worked:           | 1                      |
| Contribution to Project:               | Sample processing      |
| Funding Support:                       | NIH, DOD, V-Foundation |

|       |          |
|-------|----------|
| Name: | Yan Chen |
|-------|----------|

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|--|---|
| Project Role:                          | Research Specialist                             |
| Researcher Identifier (e.g. ORCID ID): |   |
| Nearest person month worked:           | 1   |
| Contribution to Project:               | Genomics, molecular analysis, sample processing |
| Funding Support:                       | NIH, BCRF                                       |

|  |                      |
|--|----------------------|
| Name:                                  | Jewell Graves        |
| Project Role:                          | Research Specialist  |
| Researcher Identifier (e.g. ORCID ID): |                      |
| Nearest person month worked:           | 1                    |
| Contribution to Project:               | Flow cytometry assay |
| Funding Support:                       | DOD, NIH             |

|  |                         |
|--|-------------------------|
| Name:                                  | Joseph Kim              |
| Project Role:                          | Research Specialist     |
| Researcher Identifier (e.g. ORCID ID): |                         |
| Nearest person month worked:           | 2                       |
| Contribution to Project:               | CTC, DTC assays         |
| Funding Support:                       | BCRF, DOD, V-Foundation |

|  |                          |
|--|--------------------------|
| Name:                                  | Francesco Elia Marino    |
| Project Role:                          | Post-Doctoral Researcher |
| Researcher Identifier (e.g. ORCID ID): |                          |
| Nearest person month worked:           | 9                        |
| Contribution to Project:               | ptDNA, CTC, DTC assays   |
| Funding Support:                       | NIH, DOD                 |

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|--|----------------------------|
| Name:                                  | Nathan Mears               |
| Project Role:                          | Research Specialist        |
| Researcher Identifier (e.g. ORCID ID): |                            |
| Nearest person month worked:           | 2                          |
| Contribution to Project:               | Mouse breeding, genotyping |
| Funding Support:                       | NIH, DOD, BCRF             |

|               |              |
|---------------|--------------|
| Name:         | Dhruv Pant   |
| Project Role: | Data Analyst |

|  |                              |
|--|------------------------------|
| Researcher Identifier (e.g. ORCID ID): |                              |
| Nearest person month worked:           | 2                            |
| Contribution to Project:               | Genomic data analysis        |
| Funding Support:                       | NIH, DOD, V-Foundation, BCRF |

|  |   |
|--|---|
| Name:                                  | Tien-Chi Pan                                |
| Project Role:                          | Data Analyst                                |
| Researcher Identifier (e.g. ORCID ID): |   |
| Nearest person month worked:           | 1   |
| Contribution to Project:               | Genomic data analysis, statistical analysis |
| Funding Support:                       | NIH, DOD, V-Foundation, BCRF                |

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|--|--|
| Name:                                  | Judith Ann Smith                                   |
| Project Role:                          | Research Project Manager                           |
| Researcher Identifier (e.g. ORCID ID): |  |
| Nearest person month worked:           | 1  |
| Contribution to Project:               | Laboratory management, sample repository oversight |
| Funding Support:                       | NIH, DOD, V-Foundation, BCRF                       |

|  |   |
|--|---|
| Name:                                  | Christopher Sterner   |
| Project Role:                          | Research Project Manager  |
| Researcher Identifier (e.g. ORCID ID): |   |
| Nearest person month worked:           | 1   |
| Contribution to Project:               | Mouse experimentation, breeding, genotyping, technician supervision |
| Funding Support:                       | NIH, DOD, V-Foundation, BCRF  |

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
  - Yes - Other Support for Dr. Chodosh and Dr. DeMichele is attached.
- **What other organizations were involved as partners?**
  - Nothing to report

## 8. SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS:** *For collaborative awards, independent reports are required from **BOTH** the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ers.amedd.army.mil> for each unique award.*
  - **QUAD CHARTS:** *If applicable, the Quad Chart (available on <https://www.usamraa.army.mil>) should be updated and submitted with attachments.*
9. **APPENDICES:** *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc. Reminder: Pages shall be consecutively numbered throughout the report. **DO NOT RENUMBER PAGES IN THE APPENDICES.***

## DEMICHELE, ANGELA

### ACTIVE:

**P30 CA016520 (Vonderheide,R)** 12/01/10 – 11/30/20 1.20 Calendar  
NIH \$24,849  
University of Pennsylvania Cancer Center Core Grant

Funding for Dr. DeMichele's role as co-director of the Breast Cancer Program in the University of Pennsylvania Cancer Center.

**R01 CA197000 (Kontos,D)** 04/19/16 – 03/31/21 0.42 Calendar  
NIH \$7,585  
Multi-Parametric 4-D Imaging Biomarkers for Neoadjuvant Treatment Response

We propose to develop new computational tools to extract multi-parametric spatio-temporal imaging signatures that can potentially constitute powerful biomarkers and comprehensively characterize their longitudinal change during treatment via 4D deformable image registration, as predictors of response to neoadjuvant chemotherapy for breast cancer.

**R01 CA208273 (DeMichele, A/Chodosh, L)** 12/13/16 – 11/30/21 1.50 Calendar  
NIH \$100,450  
Secondary Prevention through Surveillance and Intervention

The ability of residual breast cancer cells to survive surgery, radiation adjuvant therapy and persist for years in the bone marrow and other sites is a critical determinant of breast cancer outcome, since these "disseminated cancer cells"(DTCs) give rise to metastatic disease that is currently incurable. In this proposal we will build upon our discoveries in mouse models of how to effectively kill residual cancer cells by conducting a new kind of clinical trial aimed at targeting and eliminating these cells, coupled with the development of an improved testing approach to identify those women who have DTCs.

**R01 HL134905 (Kawut,S)** 01/01/17 – 12/31/21 0.36 Calendar  
NIH \$7,454  
Anastrozole in Pulmonary Arterial Hypertension (AIPH2)-CCC  
Project Narrative Anastrozole is a generic drug which has been FDA-approved for breast cancer for twenty years and has an excellent safety profile. We propose a Phase II randomized, double-blind, placebo-controlled trial of anastrozole in 84 post-menopausal women and men with PAH for one year to determine if anastrozole increases the six-minute walk distance.

**N/A (DeMichele, A)** 07/01/15 – 06/30/20 2.40 Calendar  
QuantumLeap Healthcare Collaborative \$200,000  
I-SPY 2 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And moLecular Analysis 2)

Trial to determine whether adding investigational agents to standard neoadjuvant paclitaxel (with or without trastuzumab), and/or doxorubicin and cyclophosphamide, increases the probability of pathologic complete response (pCR) over standard neoadjuvant chemotherapy alone, for each biomarker signature established at trial entry, and to determine for each experimental agent used, the predictive probability of success in a subsequent phase 3 trial for each possible biomarker signature.

Subcontract: PI

**N/A (Minn,A)** 06/15/17 – 06/14/20 0.60 Calendar  
DOD \$20,444  
Combinatorial Strategies to Overcome Resistance to Immune Checkpoint Blockade in Breast Cancer

Project to examine role of JAK/STAT blockade in overcoming resistant to immunological checkpoint inhibitors in breast cancer.

**P01 CA210961 (Esserman, L/DeMichele, A)** 09/08/17 – 08/31/22 1.80 Calendar  
Sub to UCSF/NIH \$36,428  
I-SPY2 + : Evolving the I-SPY2 TRIAL to Include MRI-directed, adaptive sequential treatment to Optimize Breast Cancer Outcomes

This project seeks to transform the neoadjuvant I-SPY2 Trial into a trial that enables assessment of response mid-treatment and treatment modification based on that response, in order to optimize outcomes for patients receiving neoadjuvant therapy for breast cancer, and evaluate new treatment strategies.

**UPCC06115 (DeMichele,A)** 06/15/15 – 07/31/22 0.22 Calendar  
NOVARTIS \$153,806  
A Phase I Trial of LEE011 and Weekly Paclitaxel in Patients with Rb+Advanced Breast Cancer

**UPCC06116 (DeMichele,A)** 07/21/16 – 07/31/21 0.06 Calendar  
PRECOG \$48,847  
PALLAS, PALbociclib Collaborative Adjuvant Study: A randomized phase III trial of Palbociclib with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for hormone receptor positive (HR+) / human epidermal growth factor receptor 2 (HER2)-negative early breast cancer

**W81XWH-17-1-0594 (Chodosh, L/DeMichele, A)** 09/30/17 – 09/29/20 1.20 Calendar  
DOD \$58,193  
Dynamic Response of Disseminated Tumor Cells & Circulating Tumor Markers to Targeted Adjuvant Therapy

The goal of these studies is to understand the properties of dormant residual tumor cells at local and distant sites in a HER2 mouse model.

**N/A (DeMichele, A)** 11/09/12 – 11/08/22 <0.12 Calendar  
Genentech \$4,405,800  
A Randomized Multicenter, Double-Blind, Placebo-Controlled Comparison of Chemotherapy Plus Trastuzumab Plus Placebo Versus Chemotherapy Plus Trastuzumab Plus Pertuzumab As Adjuvant Therapy in Patients with Operable Her2-Positive Primary Breast Cancer

**OVERLAP:** There is no scientific or budgetary overlap. Support will not be permitted to exceed 12.00 CM. In the unlikely event that over 12.00 CM support were attained, then the work on support from existing projects would be adjusted downward, with other faculty or staff assuming additional duties on each project.