AWARD NUMBER: W81XWH-18-1-0491

TITLE: Targeting CDK4/6 in HER2-positive breast cancer brain metastases

PRINCIPAL INVESTIGATOR: Jean J. Zhao, PhD

CONTRACTING ORGANIZATION: Dana-Farber Cancer Institute
Boston, MA 02215

REPORT DATE: September 2019

TYPE OF REPORT: Annual

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
September 2019	Annual	1 Sep 2018 – 31 Aug 2019

4. TITLE AND SUBTITLE
Targeting CDK4/6 in HER2-positive breast cancer brain metastases

5a. CONTRACT NUMBER

5b. GRANT NUMBER W81XWH-18-1-0491

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

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

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The purpose of this project is to use patient-derived xenograft (PDX) models and genetically-engineered mouse models (GEMMs) of HER2+ breast cancer brain metastases (BCBM) to test novel CDK4/6-based combination therapies for activity against HER2+ BCBM. By using anti-CDK4/6 drugs with other targeted therapies we will be able test the potential synergy of drug combinations against HER2+ BCBM.

Due to pending approval of involving human subjects, we do not have any activities to report on using patient derived xenograft (PDX) models. However, we have made a considerable progress in mouse tumor cells and syngeneic mouse models of BCBM. Our positive preliminary results from mouse models laid the foundation for further developing effective therapeutic strategies against specific subtypes of breast cancer brain metastases, which is important for deliver pre-clinical information to guide the rational design of promising clinical trials.

15. SUBJECT TERMS
HER2+ breast cancer, brain metastases, targeted therapy, immunotherapy, combination therapy, CDKN2A/2B, CDK4/6-Rb pathway, therapeutic resistance, immune checkpoint blockade, syngeneic GEMM, PDX, HER2 inhibitor, CDX4/6 inhibitor

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	13	19b. TELEPHONE NUMBER *(include area code)*

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1. INTRODUCTION:

Breast cancer brain metastases (BCBM) remain a significant clinical challenge. This is especially true for patients with the HER2+ subtype of breast cancer where up to half of patients with metastatic disease eventually develop brain metastases. To date, there are no FDA-approved systemic therapies for the specific treatment of breast cancer brain metastases. Through careful molecular and genetic analysis of HER2+ BCBM patient samples we identified a high frequency *CDKN2A/2B* copy number loss in HER2+ BCBMs, suggesting hyperactivation of the CDK4/6-Rb pathway. We hypothesize that hyperactivation of the CDK4/6-Rb pathway in HER2+ BCBMs, via loss of *CDKN2A/2B*, would be vulnerable to treatment with CDK4/6 inhibitors whose activity maybe synergized in combination with immune therapies. This proposal is designed to investigate the efficacy of targeting CDK4/6 in HER2+ BCBM and develop CDK4/6-inhibitor based combinations with immune checkpoint blockade to treat HER2+ BCBM. In this study, we propose to use patient derived xenograft (PDX) models and syngeneic genetically-engineered mouse models (GEMMs) of HER2+ BCBM to test novel CDK4/6-based combination therapies for activity against HER2+ BCBM.

2. KEYWORDS:

HER2+ breast cancer, brain metastases, targeted therapy, immunotherapy, combination therapy, CDKN2A/2B, CDK4/6-Rb pathway, therapeutic resistance, immune checkpoint blockade, syngeneic GEMM, PDX, HER2 inhibitor, CDX4/6 inhibitor

3. ACCOMPLISHMENTS

3a. What were the major goals of the project?

- Specific Aim 1: to investigate the effects of combined CDK4/6 and HER2 inhibition in HER2-positive BCBM.
    - Major Task 1. To determine whether CDKN2A/2B status in HER2+ BCBM dictates response to CDK4/6 inhibition, and to evaluate the efficacy of CDK4/6 inhibition in combination with HER2-targeted therapy. (No activity)
    - Major Task 2. To evaluate the therapeutic response of HER2+ ER- BCBM to CDK4/6 inhibition in combination with HER2-targeted therapy. (No activity)

- Specific Aim 2: To investigate the effects of CDK4/6 inhibition on anti-tumor immunity in HER2-positive BCBM
    - Major Task 1: To determine the effects of CDK4/6 inhibition on HER2+ BCBM tumors autonomous immune response. (No activity)
    - Major Task 2. To evaluate whether combinations of CDK4/6 inhibition with immunomodulatory agents have CNS efficacy in syngeneic GEMMs of HER2+ BCBM tumors.
        - Subtask 1. Generate MMTV-Neu-IRES-Cre / PtenL/L (NIC/Pten) Cdkn2a-/- or Cdkn2b-/- (NIC/Pten/Cdkn) syngeneic tumors using in vitro CRISPR gene editing of NIC/Pten tumor cells (1-12 months, completed)
        - Subtask 2. Establish NIC/Pten/Cdkn and NIC/Pten orthotopic brain tumors by intracranial injection into syngeneic FVB female mice (12-24 months, completed)
        - Subtask 3. Treat NIC/Pten intracranial tumor bearing mice with 4 arms: abemaciclib or PD1 inhibitor or abemaciclib + PD1 inhibitor or vehicle measure response by change in tumor volume using bioluminescence and animal survival (18-24 months, ~50% completion)

3b. What was accomplished under these goals?

Aim 2 - Subtask 1. Generate MMTV-Neu-IRES-Cre / PtenL/L (NIC/Pten) and NIC/Pten/Cdkn syngeneic tumors using *in vitro* CRISPR gene editing of NIC/Pten tumor cells.

We have carried out successful CRISPR-mediated gene ablation of Cdkn2a in NIC/Pten^{null} brain mets tumor cells as shown in Figure 1 panel A. Interestingly, while NIC/Pten^{null} tumor cells have Cdkn2a mRNA expression, the p16 protein level was not detectable by WB analysis (Figure 1 B), suggesting a post transcription loss of p16 in NIC/Pten^{null} tumor cells. Hereafter, NIC/Pten^{null} tumor cells are labeled as NIC/Pten^{null}/p16^{null} tumor cells.

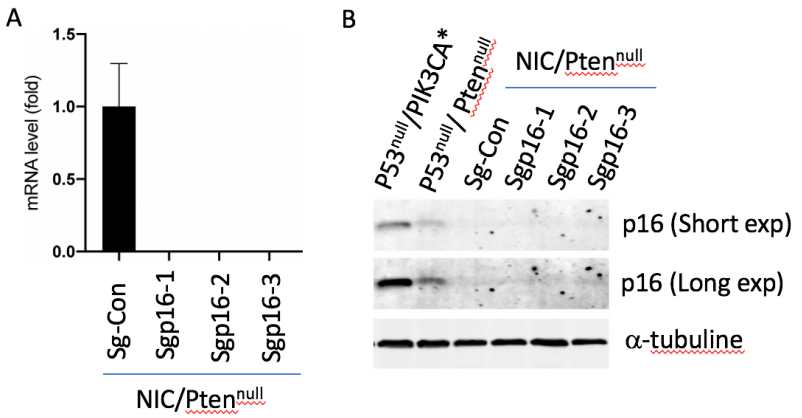

Figure 1. CRISPR-mediated deletion of Cdkn2a in NIC/Pten^{null} BCBM tumor cells. (A). Expression levels of mRNA in sg-control and 3 sgRNA against p16Ink4a (Cdkn2a). (B) Western blotting analysis of Cdkn2a-KO NIC/Pten^{null} KO cells. P53^{null}/PIK3CA* and P53^{null}/Pten^{null} mouse mammary tumor cells used as controls.

Alternative approach: We plan to introduce Cdkn2a into NIC/Pten^{null}/p16^{null} cells to make NIC/Pten^{null}/p16+ tumor cells to evaluate the effect of the presence and absence of p16 on the therapeutic response to CDK4/6 inhibition.

Aim 2 - Subtask 2. Establish NIC/Pten/Cdkn and NIC/Pten orthotopic brain tumors by intracranial injection into syngeneic FVB female mice.

We have established NIC/Pten^{null}/p16^{null} orthotopic brain tumor models via both intracranial injection and intracarotid injection methods (Figures 2 and 3 and not shown). We have proceeded to Subtask 3 on evaluation of therapeutic responses to CDK4/6 inhibitor, HER2 inhibitor and PD-1 blockade and their combinations.

Aim 3 - Subtask 3. Treat NIC/Pten^{null}/p16^{null} intracranial tumor bearing mice with various inhibitors and combinations, and measure responses by change in tumor volume using bioluminescence and animal survival.

We started with treatment of a cohort of NIC/Pten^{null}/p16^{null} intracranial tumor allograft-bearing mice with CDK4/6 inhibitor (abemaciclib) and HER2 inhibitor (ONT380, tucatinib). Both of these drugs have potent brain penetration. As shown in Figure 2, while tucatinib had some activity as a single agent, the combination of tucatinib and abemaciclib had a greater effect on survival benefit. We have also tested the combination of abemaciclib and PD1 blockade as shown in Figure 3. These results show that these combination therapeutic approaches are able to extent the survival of brain tumor bearing animals, more combinations of targeted therapy and immunotherapy are needed to identify most effective therapy to improve the therapeutic outcome, e.g. stable remission or eradication of tumor cells.

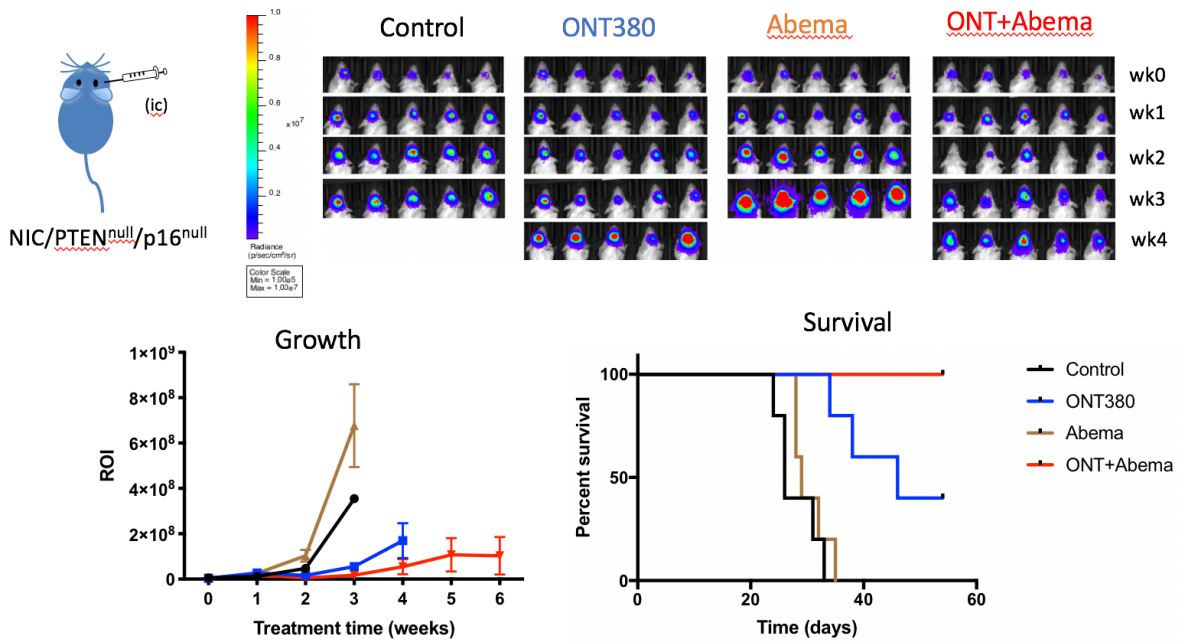

Figure 2. Combination of CDK4/6 inhibitor (abemaciclib) and HER2 inhibitor (ONT380, tucatinib) on NIC/Pten^{null}/p16^{null} intracranial tumor bearing mice.

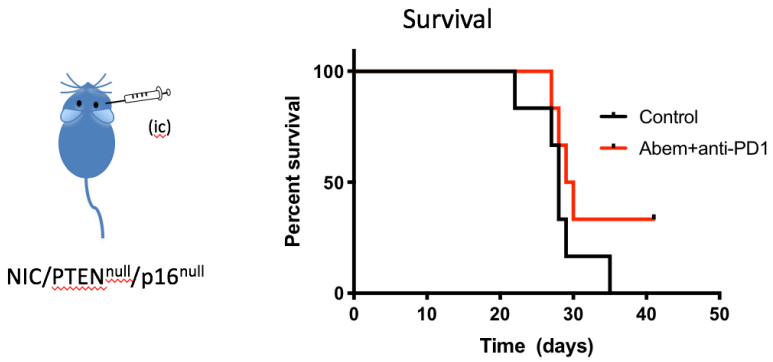

Figure 3. Combination of CDK4/6 inhibitor (abemaciclib) and anti-PD1 mouse antibody on NIC/Pten^{null}/p16^{null} intracranial tumor bearing mice.

3c. What opportunities for training and professional development has the project provided?

Nothing to Report.

3d. How were the results disseminated to communities of interest?

Nothing to Report

3e. What do you plan to do during the next reporting period to accomplish these goals?

We recently received the notice from USAMRDC Office of Research Protections (ORP) that ORP Human Research Protection Office (HRPO) concurs with the DFCI IRB Office's determination of research not involving human subjects (IRB Study Number 19-420, Proposal Number BC171657, Award Number W81XWH-18-1-0491, 9/17/2019). With this approval, we plan to proceed our project with a major effort on working with PDX models as described in the proposal. Specifically, we will move ahead immediately with these tasks outlined in the SOW under the Specific Aim 1 to investigate the effects of combined CDK4/6 and HER2 inhibition in HER2-positive BCBM using PDX models established at DFCI during the next reporting period to accomplish the goals and objectives.

4. IMPACT *Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to the items below:*

4a. What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report.

4b. What was the impact on other disciplines?

Nothing to Report.

4c. What was the impact on technology transfer?

Nothing to Report.

4d. What was the impact on society beyond science and technology?

Nothing to Report.

5. CHANGES/PROBLEMS

5a. Changes in approach and reasons for change:

Nothing to Report.

5b. Actual or anticipated problems or delays and actions or plans to resolve them:

Work with PDX models was delayed as the necessary HRPO approval for use of human materials took significantly longer to complete than originally anticipated. However, the approval is now in place and we are moving ahead with the research plan as expediently as possible.

5c. Changes that had a significant impact on expenditures:

Expenditures in the initial year of this grant have been lower than originally budgeted due to the delays encountered in receiving HRPO approval for use of human materials. The approval is now in place and our rate of expenditure will increase accordingly.

5d-f. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents:

5d. Significant changes in use or care of human subjects: *Nothing to Report.*

5e. Significant changes in use or care of vertebrate animals: *Nothing to Report.*
5f. Significant changes in use of biohazards and/or select agents: *Nothing to Report.*

6. PRODUCTS *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

Nothing to Report.

6a. Publications, conference papers, and presentations:

Nothing to Report.

6b. Website or other internet site:

Nothing to report.

6c. Technologies or techniques:

Nothing to report.

6d. Inventions, patent applications, and/or licenses:

Nothing to report.

6e. Other Products:

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

7a. What individuals have worked on the project? *(1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period.*

Name: Jean Zhao
Project Role: PD/PI
Researcher Identifier (ORCID): 0000-0002-4561-5688
Nearest person month worked: 1
Contribution to project: Responsible for overall research design and supervision.
Funding support: This award

Name: Tao Jiang
Project Role: Staff Scientist
Researcher Identifier (ORCID): none
Nearest person month worked: 4
Contribution to project: Mouse modeling and in vivo treatment.
Funding support: This award

Name: Jing Ni
Project Role: Staff Scientist
Researcher Identifier (ORCID): none

Nearest person month worked: 4
Contribution to project: Mouse modeling and in vitro molecular and cellular biology.
Funding support: This award

7b. Has there been a change in the active other support of the PD/PI or senior/key personnel since the last reporting period?

If the active support has changed for the PD/PIs or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously.

Yes. There have been several changes to the active support of Dr. Jean Zhao since it was last reported:

PREVIOUSLY ACTIVE AWARDS, NOW CLOSED:

5 P50 CA168504-05 (Winer) 09/17/13 – 07/31/18 7.5% effort
NIH $72,807 (Zhao lab, annual direct costs)
DF/HCC SPORE in Breast Cancer, Project 2: Overcoming resistance to standard HER2-directed therapies for breast cancer

Goals: The goals of Project 2 are to identify and overcome both PI3K- dependent and independent mechanisms of resistance to targeted therapy of HER2+ breast cancer.

Specific Aims: To optimize the application of PI3K-directed therapies, both in novel genetically engineered mouse (GEM) models and subsequently in a clinical trial. Since a combination of anti-HER2 therapy and PI3K inhibition will likely be ineffective for some patients due to additional mutations bypassing the HER2/PI3K pathway, we will utilize recently developed methods to study mechanisms of resistance that lie outside the PI3K pathway.

Funding Agency Contact: Jason Gill, NCI, gillgas@mail.nih.gov

(Zhao and Wang) 10/01/15 – 09/30/18 7.5% effort
Breast Cancer Research Foundation $208,333 (annual direct costs)
Targeting PTEN deficiency in metastatic breast cancer with PI3K inhibition in combination with immunotherapy

Goals: In this grant year, we plan to continue our investigation on PTEN-deficient metastatic breast cancer with a focus on developing combinations of PI3K targeted therapy and immunotherapy.

Specific Aims: 1) To develop combination therapies of PI3K-p110beta inhibition with immune checkpoint blockade in PTEN-deficient metastatic breast cancer; and 2) evaluation of therapeutic approaches targeting PI3K/mTOR in combination with immune checkpoint blockade in breast cancer brain metastases.

Funding Agency Contact: Sarah Boll, The Breast Cancer Research Foundation, sboll@bcrfcure.org

(Lin) 10/01/13 – 09/30/18 1.5% effort
Breast Cancer Research Foundation $62,649 (annual direct costs, Zhao lab)
Improving Therapeutic Options for Metastatic Breast Cancer

Goals: The aim of this research is to study novel approaches to treating brain metastases in patients with breast cancer and to identify resistance mechanisms in metastatic breast cancer.

Specific Aims: 1) to evaluate and develop new treatment options for patients with breast cancer brain metastases; 2) to identify resistance mechanisms operative in human breast cancers.

Funding Agency Contact: Sarah Boll, The Breast Cancer Research Foundation, sboll@bcrfcure.org

5 P50 CA165962-05 (Batchelor) 09/19/13 – 05/31/19 7.5% effort
NIH/NCI $178,700 (Roberts & Zhao labs, annual direct costs)

SPORE in Brain Cancer: Targeted Therapies for Gliomas
Project 2: Targeting the PI3K signaling axis

Goals: The broad goal of Project 2 is to use the data and clinical materials from patients on our BKM120 trial- in concert with human tumor derived primary neurosphere cultures and genetically defined mouse models – to address three important unresolved questions involving PI3 kinase inhibitors as glioblastoma therapeutics.

Specific Aims: Aim 1. To evaluate the impact of GBM genetic modifiers on response to BKM120. Aim 2. To assess the impact of BKM120 in combination with radiotherapy (RT) and temozolomide (TMZ), as well as in combination with other rational targeted therapies, on GBMs. Aim 3. To determine which of the two common isoforms of PI3K (p110α or p110β) is the driving force behind PTEN null GBMs in order to identify potential effective isoform specific inhibitors for GBM

Funding Agency Contact: (Subaward from Massachusetts General Hospital) Ashley McNulty, almcnutly@partners.org

Sponsored Research Agreement (Zhao) 06/23/16 – 06/22/18 3.0% effort
Lilly-DFCI/DFPCC Collaboration Program $187,930 (direct costs)
Evaluating CSF1Ri LY3022855 and CS7 in PDX and GEM models of breast cancer

Goals: To assess the therapeutic efficacy of antibody based agents in breast cancer using novel preclinical
models.

Specific Aims: 1) Evaluating LY3022855 and CS7 using PDX models derived from metastatic breast cancer; 2) Evaluating CS7 using GEM models of breast cancer.

Funding Agency Contact: Nancy Grodin, Belfer Office for Dana-Farber Innovations, Dana-Farber Cancer Institute, nancy_grodin@dfci.harvard.edu

(Zhang and Zhao) 08/01/16 – 07/31/18 0% effort*
Dana-Farber/Northeastern Joint Program in Cancer Drug Development $25,000 (Zhao lab, direct costs)
Making Oligonucleotides Better Cancer Biopharmaceuticals by Steric Protection

Goals: This grant will test the hypothesis that because most unwanted side effects of nucleic acids are initiated by specific or non-specific protein recognition, blocking protein access while maintaining nucleic acid hybridization is the key to addressing the difficult biopharmaceutical challenges of nucleic acid drugs.

Specific Aims: 1) Optimization and gaining insight into fundamental materials properties (Zhang lab); and 2) Understanding in vitro and in vivo characteristics of pacDNA (Zhao lab).

Funding Agency Contact: Barrett Rollins, Chief Scientific Officer, Dana-Farber Cancer Institute, barrett_rollins@dfci.harvard.edu

**This award supported partial effort for a graduate student to carry out the proposed experiments under Dr. Zhao's supervision; no measurable portion of Dr. Zhao's own effort is required.*

W81XWH-15-0016 (Silver) 05/01/17 – 11/15/18 1.0% effort
DOD CDMRP $9,451 (annual direct costs)
Validation of MECP2 as a new therapeutic target in TNBC

Goals: In this grant we test the hypothesis that the growth of a significant percentage of TNBCs is driven by MECP2 overexpression, and that these tumors will be susceptible to less toxic therapies as a result of the unique mechanism of action of MECP2 in tumorigenesis.

Specific Aims: Dr. Zhao's laboratory will propagate the patient-derived xenograft (PDX) mouse models of breast cancer necessary for this grant, and coordinate the transfer of mice or frozen vials to the PI.

Funding Agency Contact: (Subaward from Thomas Jefferson University) Michele Cordero-Boligitz, Thomas Jefferson University, subawards@jefferson.edu

Sharpe/NBTS Award (Zhao and Wen) 08/01/17 – 07/31/18 1.0% effort
National Brain Tumor Society $25,000 (direct costs)
Developing effective therapeutics of targeted therapy and immunotherapy in GBM

Goals: To explore new opportunities for combining CDK4/6 inhibitors with a range of other

immunologic therapies for glioblastoma (GBM) patients.

Specific Aims: 1) To evaluate the effect of abemaciclib on inducing GBM tumor cells' antigen presentation capacity; and 2) evaluate the combination therapy of abemaciclib and PD-1 blockade in genetically-engineered mouse models of GBM.

Funding Agency Contact: Kacey Troy, Research and Advocacy Manager, National Brain Tumor Society, ktroy@braintumor.org.

NEW ACTIVE AWARDS:

BC170330 (Bose, Ma) 05/15/18 – 05/14/22 1% effort
DOD CDMRP $76,711 Zhao Lab Annual Direct Costs
Targeting HER2 Activating Mutations in ER-Positive, Metastatic Breast Cancer

Goals: For this grant, Dr. Zhao's laboratory will carry out the generation and therapeutic treatment of PDX models of ER+ and HER2 mutant breast cancer.

Specific Aims: 1) Conduct a phase II clinical trial of neratinib plus fulvestrant in ER+, $HER2^{mut}$ MBC; 2) Conduct a co-clinical trial using $HER2^{mut}$ patient-derived xenografts (PDX's) and a novel, $HER2^{mut}$ transgenic mouse to determine the effect of neratinib containing drug combinations and modifier genes; and 3) Identify mechanisms of acquired drug resistance using proteomics and next-generation DNA sequencing.

Funding Agency Contact: (Subaward from Washington University School of Medicine) Bill Courtney, Grant Specialist, bill.courtney@wustl.edu

Overlap: None

Sponsored Research Agreement (Zhao) 05/22/18 – 12/20/19 1% effort
Puma Biotechnology $261,143 Annual Direct Costs
Evaluating Neratinib in orthotopic PDX modles of breast cancer brain metastases

Goals: The goal of this project is to test neratinib as single agent and in combination with T-DM1, an antibody-drug conjugate ado-trastuzumad emtansine, on PDX models of HER2-positive breast cancer brain metastasis.

Funding Agency Contact: Alan Auerbach, CEO, Puma Biotechnology, Inc., 10880 Wilshire Blvd., Suite 2150, Los Angeles, CA 90024

Overlap: None

(Zhao) 10/01/19 – 09/30/20 12% effort
Breast Cancer Research Foundation $208,333 Annual Direct Costs
Integrating immunotherapy and targeted therapy for the treatment of metastatic breast cancer

Goals: In this project, we will aim to deliver on the promise of personalized medicine by developing safe and effective combinations of targeted and immunotherapies directed against specific molecular abnormalities typically found in advanced and metastatic breast cancer.

Specific Aims: Aim 1. Investigate and target mechanisms of resistance to immune response in PTEN-deficient triple-negative breast cancer (TNBC). Aim 2. Evaluate therapeutic strategies combining PARP inhibition with targeted therapies and immunotherapy in syngeneic genetically-engineered mouse models (GEMMs) with BRCA deficiency. Aim 3. Evaluate therapeutic strategies combining PARP inhibition with targeted therapies in BCBM patientderived xenograft (PDX) models with BRCA deficiency.

Funding Agency Contact: Sarah Boll, The Breast Cancer Research Foundation, sboll@bcrfcure.org

Overlap: None

(McFaline Figueroa, Zhao, Wen) 03/28/19 – 03/27/21 0% effort*
National Brain Tumor Society $25,000 Annual Direct Costs
Integrating CDK4/6 inhibition and immunotherapy for glioblastoma using humanized mouse models
Goals: We propose to determine if CDK4/6 inhibition likewise triggers anti-tumor immunity in human glioblastoma and whether it synergizes with immunotherapy in preclinical animal models of glioblastoma with

humanized immune systems.
Specific Aims: Aim 1: To determine if CDK4/6 inhibition modulates the immune tumor microenvironment in human subjects with recurrent glioblastoma. Aim 2: To determine the efficacy of and genetic modifiers of response to combination CDK4/6 inhibition and immune checkpoint blockade in humanized glioblastoma mouse models.

Funding Agency Contact: Kacey Troy Ribnik, Research and Advocacy Manager, NBTS, ktroy@braintumor.org

**This award supports effort of an Instructor in Dr. Zhao's lab to carry out the proposed experiments, and does not require any measurable portion of Dr. Zhao's own effort.*

Overlap: None

1 R01 CA233810-02 (Roberts) 09/01/18 – 11/30/19 4% effort
NIH $102,118 Zhao Lab Annual Direct Costs
Molecular mechanisms and therapeutic targeting of PI3K-p110beta/PTEN signaling in breast cancer and cancer immunity

Goals: In this project, we aim to develop novel targeted therapies against PTEN-deficient triple-negative breast cancer (TNBC).

Specific Aims: 1) To develop rationally-designed therapeutic approaches of P110beta-directed combination therapies in PTEN-deficient TNBC; 2) To elucidate the role of p110beta in PTEN loss-induced tumor immune evasion and evaluate the use of immunotherapy in combination with p110beta inhibitors in TNBC.

Funding Agency Contact: Leota Hall, National Cancer Institute, hallle@mail.nih.gov

Overlap: None

2 P50 CA168504-06A1 (Winer) 07/05/19 – 06/31/24 5% effort
NIH $168,183 Project 3 Annual Direct Costs
Dana-Farber/Harvard Cancer Center SPORE in Breast Cancer; Project 3 (Zhao and Lin – Project Leaders)

Goals: Our proposal aims to further our understanding of the unique vulnerabilities of breast cancer brain metastases and to move forward new therapeutic approaches in order to improve outcomes for this devastating site of disease involvement.

Specific Aims: Aim 1. To evaluate the role of PTEN loss, which is frequently seen in BCBM, in the growth and maintenance of HER2+ brain metastases, and to evaluate whether strategies to target the PI3K/PTEN/mTOR pathway have therapeutic effects against HER2+ BCBM. Aim 2. To evaluate the role of the cyclin D1/CDK4/Rb pathway, which is frequently activated in BCBM, in the growth and maintenance of BCBM, and to evaluate whether strategies to target the pathway have therapeutic effects in ER+/HER2- or HER2+ BCBM.

Funding Agency Contact: JoyAnn Phillips Rohan, National Cancer Institute, joyann.rohan@nih.gov

Overlap: There are some shared goals between SPORE Project 3 and DoD grant W81XWH-18-1-0491, but no overlapping work. Our DoD project entirely focuses on HER2+ BCBM with CDK4/6 inhibition using already established PDX models, whereas the SPORE project Aim 2 has some components of HER2+ BCBM with CDK4/6 blockade and will use newly established PDX models from new patients with brain metastases. W81XWH-18-0491 is focused only on the preclinical work and does not include either the clinical trial or any of the correlative studies embedded within the trial proposed in the SPORE project. There is no budgetary overlap between these two projects.

2 P50 CA165962-06A1 (Batchelor) 08/01/19 – 07/31/24 5% effort
NIH/NCI $200,000 Project 3 Annual Direct Costs
SPORE in Brain Cancer: Targeted Therapies for Glioma, Project 3 (Zhao and Wen – Project Leaders)

Goals: The goal of this project is to develop a novel rational combination therapy of CDK4/6 inhibition with immunotherapy to target specific molecular abnormalities found in majority of glioblastoma (GBM).

Specific Aims: 1) Assess the effects of CDK4/6 inhibition on GBM cell-intrinsic immune response; 2) Assess the effects of CDK4/6 inhibition on enhancing immunotherapy in syngeneic models of GBM; 3) Evaluate the impact of CDK4/6 inhibitors on immune function and clinical outcome for GBM patients.

Funding Agency Contact: (Subaward from Brigham and Women's Hospital) LaShaunda Gayden, lgayden@bwh.harvard.edu

Overlap: None

7c. What other organizations were involved as partners? *Describe partner organizations - academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) - that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.If there is nothing significant to report during this reporting period, state "Nothing to Report."*

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

Independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks must be clearly marked with the responsible PI and research site. A report must be submitted to https://ers.amedd.army.mil for each unique award.

Independent reports are being submitted by each PI.

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.*

None.