AWARD NUMBER: W81XWH-19-1-0614

TITLE: Targeting the Non-Canonical Phosphoinositide Kinases in P53 Mutant Breast Cancer

PRINCIPAL INVESTIGATOR: Brooke Emerling

CONTRACTING ORGANIZATION: Sanford Burnham Prebys Medical Discovery Institute

REPORT DATE: Sept 2020

TYPE OF REPORT: Final

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
Sept 2020	Final	15 Aug 2019 – 31 May 2020

4. TITLE AND SUBTITLE

Targeting the Non-Canonical Phosphoinositide Kinases in P53 Mutant Breast Cancer

5a. CONTRACT NUMBER
W81XWH-19-1-0614

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Brooke Emerling, PhD

E-Mail: bemerling@sbpdiscovery.org

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

Sanford Burnham Prebys Medical
Discovery Institute
10901 North Torrey Pines Road
La Jolla, CA 92037-1005

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 ultimate goal and the overall impact of this project are to characterize PI5P4Ks as a novel liability for breast tumors with TP53 mutations in order to define opportunities for therapeutic intervention for breast cancer patients with these mutations, which currently lack targeted therapy.

15. SUBJECT TERMS
p53, phosphoinositide kinases, breast cancer, autophagy, metabolism, synthetic lethal

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		19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

Page

1. INTRODUCTION

The most frequently mutated gene across all types of cancers is *TP53* (encoding p53). Unfortunately, it has proven difficult to directly target p53 with drugs. I have identified a novel class of phosphoinositide kinases, the non-canonical type II phosphatidylinositol-5-phosphate 4-kinases (PI5P4Ks), whose loss of function results in synthetic lethality with p53 loss. Targeting these enzymes with novel agents could potentially prevent the growth of p53 mutant cancers, thereby benefiting a broad spectrum of cancer patients, including those with breast tumors. Prior to this observation of this synthetic lethality, these enzymes were not a focus for oncology research, and since my discovery I have been working arduously to elucidate the role of the PI5P4Ks in metabolic control. Recently, using mouse embryonic fibroblasts (MEFs), I discovered a role for the PI5P4Ks in autophagy and, for the first time, showed that these enzymes localize to lysosomes, suggesting that the PI5P4Ks may be important for lysosome function, as well as shedding light on the anti-cancer mechanism of PI5P4K inhibition in p53 deficient cancers. The goals of this proposal are two-fold: first, to continue to evaluate the role of the PI5P4Ks in the growth of p53 mutant breast cancers, and, second, to dissect the metabolic consequences upon targeting the enzymes, which will be essential in developing successful PI5P4K inhibitors for cancer treatment.

To achieve these goals, preclinical studies in novel genetically engineered mouse tumor models and human breast cancer cells will be used in order to continue to define the physiological functions of these "druggable" enzymes, to elucidate the biochemical mechanism(s) by which they regulate autophagy and cancer metabolism, and to investigate whether targeting the PI5P4Ks would be an effective therapy for *TP53* mutant breast cancers. My overarching hypothesis is that the PI5P4Ks act as sensors of metabolic stress that allow cells to modulate lysosomal events, including autophagy, in order to maintain cellular homeostasis. Further, I posit that the PI5P4Ks provide a backup to p53 with regard to mediating responses to metabolic stress and that these enzymes become critical when p53 function is lost in breast tumor cells.

2. KEYWORDS

PI5P4Ks
p53
phosphoinositide kinases
breast cancer
autophagy
metabolism
synthetic lethal
lysosome
TFEB
mTORC1

3. ACCOMPLISHMENTS

What were the major goals of the project?

The **first goal** of this project was to provide proof-of-concept that targeting *PIP4K2A* and/or *PIP4K2B* would be an effective therapy for *TP53* mutant breast cancers. A **second goal** was to develop novel breast cancer mouse models in order to determine the impact of PI5P4K suppression/deletion on tumorigenesis in mouse models of breast cancer. The **third goal** was to decipher the biochemical mechanism(s) by which loss of PI5P4Ks prevents p53 mutant breast cancer.

What was accomplished under these goals?

To date we have shown that mouse embryonic fibroblasts (MEFs) and breast cancer cell lines with wild type *TP53* are unaffected by knockout or knockdown of PI5P4Kα and PI5P4Kβ, while breast cancer cell lines with mutant p53 stop growing or die. We have now successfully screened a large panel of breast cancer cell lines, all with mutant p53, and observe a decrease in proliferation or cell death. In order to accomplish this, we have generated both stable inducible shRNA knockdown and CRISPR knockout breast cancer cell lines with either a

loss of function (LOF) or gain of function (GOF) *TP53* mutation. For example, **Figure 1** shows the inhibition of cell growth in both MDA-MB-453 (p53-LOF) and HCC38 (p53-GOF) breast cancer cells upon knockdown of the PI5P4Ks.

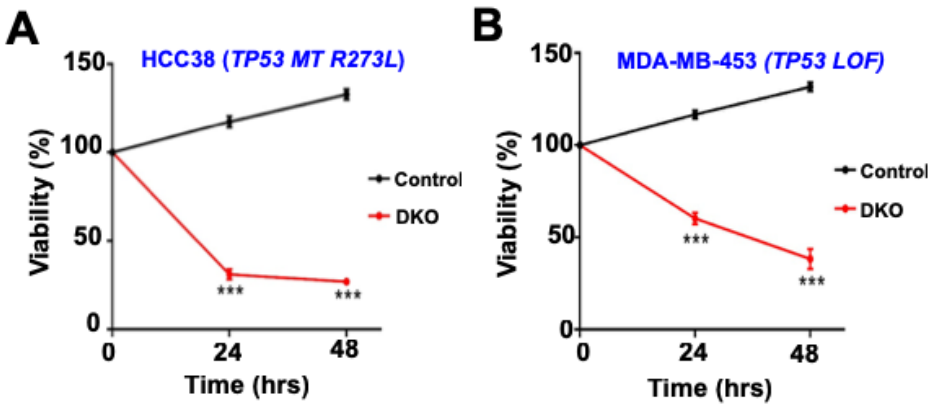

Figure 1. Knockdown of PI5P4Ks inhibits proliferation of p53 mutant TNBC cells*. PI5P4Kα and PI5P4Kβ were stably knocked down using an inducible lentiviral system in (**A**) HCC38 and (**B**) MDA-MB-453 cells. Viability and proliferation were measured 24 h and 48 h post dox treatment using the MTT assay. In all panels, means ± SD shown, n ≥ 8. Statistical significance determined using a paired, two-tailed t test (*p ≤ 0.0005).*

To note, these approaches were time-consuming and complicated as most of the breast cancer cell lines did not tolerate knockout out the PI5P4Ks using CRISPR as well as due to the lethality of PI5P4K with mutant p53 we had to generate all lines to be inducible knockdown or knockout.

To uncover the molecular mechanism(s) by which loss of PI5P4Ks prevents p53 mutant breast cancer cell growth, we recently discovered that the PI5P4K enzymes are required for autophagy. This work was published in *Molecular Cell* and I was the lead and corresponding author. In this paper we took a purely genetic approach and used only MEFs in order to decipher the biochemical mechanisms that these essential enzymes regulate when p53 function is lost. Now we are performing all the autophagy experiments we did in the MEFs in the shRNA and CRISPR inducible breast cancer cell lines that we just completed generating.

Next, we have begun to assess the role of PI-4,5-P_2 at lysosomes in breast cancer cells and we imaged PI-4,5-P_2 in several p53 mutant TNBC cell lines and preliminary results show significant co-localization between PI-4,5-P_2 and the lysosome marker LAMP1 in all lines tested thus far (**Figure 2**).

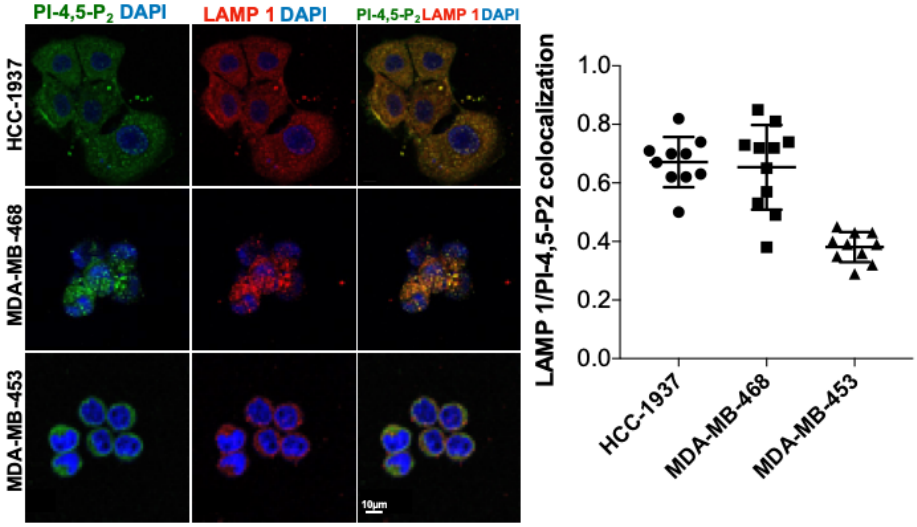

Figure 2. PI-4,5-P_2 localizes at lysosomes in TNBC cells. *Using a specific PI-4,5-P_2 antibody significant co-localization was visualized between PI-4,5-P_2 (green) and the lysosome marker LAMP1 (red) in HCC-1937 (upper panel), MDA-MB-468 (middle panel) and, to a lesser extent, MDA-MB-453 (lower panel). Colocalization quantification was performed using ImageJ and are represented in the adjacent graph as Pearson Correlation Coefficient. The data is presented as an average of n≥10 images, containing 2-4 cells, for each group. Error bars represent standard deviations.*

For our future studies we will test whether PI5P4K catalytic activity is required for autophagosome-lysosome fusion. We have preliminary evidence in MEFs that indeed the kinase activity of the PI5P4Ks are necessary for autophagosome-lysosome fusion (**Figure 3**), indicating for the ***first time*** that the production of PI-4, 5-P_2 at the lysosome is critical for

autophagosome-lysosome fusion as well as implying the involvement of the lipid for the survival of p53 mutant cells.

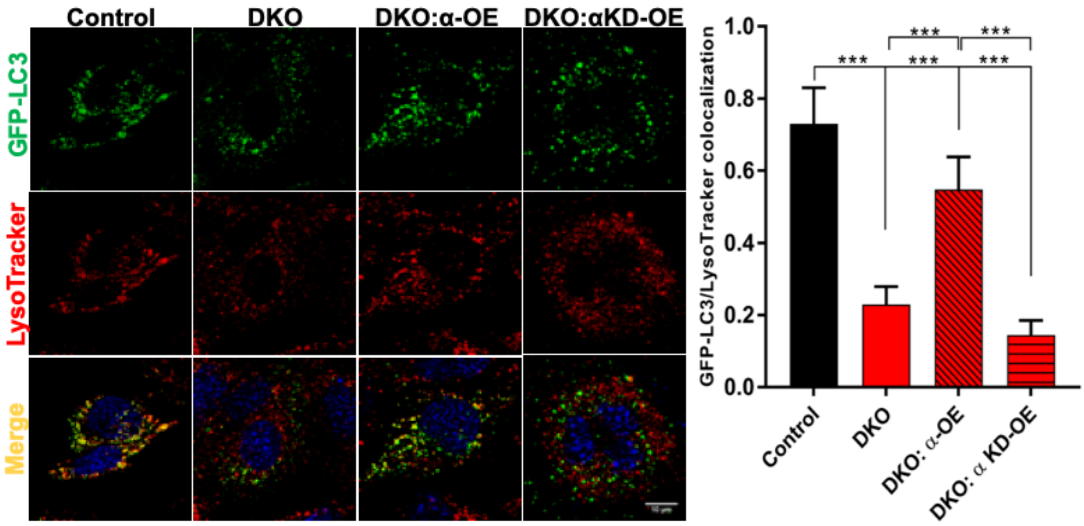

Figure 3. PI5P4K catalytic activity is required for autophagosome-lysosome fusion. *Control, DKO, DKO overexpressing WT PI5P4Kα and PI5P4Kα kinase-dead (KD) mutant MEFs were generated to stably express GFP-LC3. Cells were stained with LysoTracker Deep Red and Hoechst 33342 and imaged live on Zeiss LSM710 at 63x. Scale bars, 10 μm. Representative images showing DAPI (blue), GFP-LC3 (green) and LysoTracker Deep Red (red) puncta in control, DKO, DKO: α-overexpression (OE) and DKO: α KD-overexpression MEFs (left). Quantification of GFP-LC3/LysoTracker colocalization (right). A Pearson correlation was calculated between the puncta for the GFP-LC3 and LysoTracker immunofluorescence signal. Statistical significance determined by ANOVA (***$p \leq 0.0005$.), $n \geq 15$ with Dunnett multiple comparison post-test.*

Further, we are optimizing LysoIP, a pull-down technique that uses lysosome-specific tagged proteins to isolate the lysosome from the rest of the cellular compartments. We have successfully generated tagged TNBC lines with WT PI5P4K (**Figure 4**) and now are establishing the stable PI5P4K knockdown lines. Therefore, we will soon be poised and ready to identify lysosome-specific signalomes and metabolites, comparing the differences in the breast cancer cells lacking the PI5P4K isoforms in p53 WT versus p53 MT cells.

Lastly, we have finally developed the complex and relevant mouse model systems to study the *in vivo* effects of targeting the PI5P4Ks. We have successfully generated all the following cohorts (15 animals/group) and are currently monitoring for tumor growth.

1. *Ubc-CreERT2 Trp53$^{flx/flx}$*
2. *Ubc-CreERT2 Trp53$^{flx/flx}$ Pip4k2a$^{flx/flx}$ Pip4k2b$^{-/-}$*
3. *Ubc-CreERT2 Trp53$^{LSL\text{-}R270H}$*
4. *Ubc-CreERT2 Trp53$^{LSL\text{-}R270H}$ Pip4k2a$^{flx/flx}$ Pip4k2b$^{-/-}$*
5. *Ubc-CreERT2 Trp53$^{LSL\text{-}R172H}$*
6. *Ubc-CreERT2 Trp53$^{LSL\text{-}R172H}$ Pip4k2a$^{flx/flx}$ Pip4k2b$^{-/-}$*

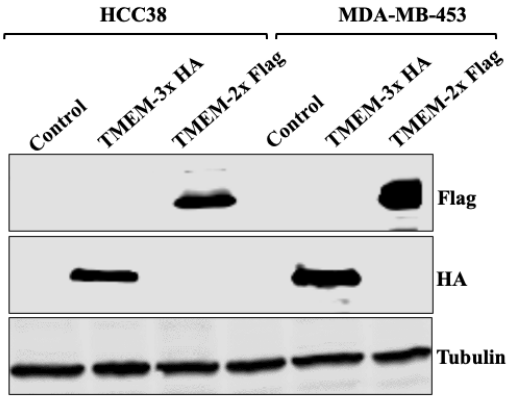

Figure 4. Establishment of p53 mutant breast cancer cell lines for Lyso-IPs. *TNBC lines (HCC38 and MDA-MB-453) which stably express lysosome-specific protein (TMEM192) tagged with either HA or Flag. Tubulin is loading control. Isolated lysosomes will then be subjected to lipidomics, proteomics and metabolomics.*

To date 4 animals (2 *Ubc-CreERT2 Trp53*$^{flx/flx}$, 2 *Ubc-CreERT2 Trp53*$^{\text{LSL-R270H}}$) have developed tumors and had to be euthanized. Excitingly, currently no animals with PI5P4K loss have any evidence of cancer.

We have also finally generated pure FVB/N mouse breast cancer models. We had to backcross (6 generations in total) our models and sent to Charles River to validate with a SNP array. We are now starting to perform the intraductal injections of adenoviral Cre into both, *Pip4k2a*$^{flx/flx}$ *Pip4k2b*$^{-/-}$ *Brca1*$^{flx/flx}$ *Trp53*$^{flx/flx}$ and *Brca1*$^{flx/flx}$ *Trp53*$^{flx/flx}$ models.

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

The Sanford Burnham Prebys Medical Discovery Institute's (SBP) Graduate School of Biomedical Sciences (GSBS) oversees and coordinates an annual individual development planning (IDP) process for all graduate students in the SBP GSBS program. The focus of the IDP process within GSBS is the development of the educational pathway of the student through identification of the skills, knowledge, and accomplishments that will be necessary for the student to obtain a PhD. degree; and identification of educational and professional development opportunities that are available for the student to obtain the necessary skills and knowledge. GSBS provides guidance and advising to both students and PIs throughout the student's education with respect to developing IDPs and preparing for a successful transition to the next career level post graduation.

The SBP GSBS IDP process includes two components:

1) **Student Mentor Annual Reports.** Each year students are required to submit an annual progress report in collaboration with their mentor. This report focuses on the educational goals accomplished through the past school year, highlights the scientific research progress and other accomplishments made by the students, and outlines an academic and research plan for the following year. Students and their mentor complete this form together and each complete sections providing feedback on the topics above. These reports are reviewed by the Graduate Program Executive Committee (GPEC) each year.

2) **Annual Thesis Committee Meetings.** Beginning in year two of studies, students are required to assemble their Thesis Committee for an annual meeting to be held between June – October of each year. At these meetings, the student outlines their current specific aims for their thesis project, reports progress made in the previous year and outlines a plan for the future of the project. The thesis committee members provide the student feedback and guidance on the progression of the research project and may suggest additional coursework or training if needed. At the completion of the meeting, the student submits a report signed by the faculty mentor containing a summary of the work they presented, the committee's feedback and plans for continuance to the Graduate Office. This report is then reviewed by GPEC.

Ryan Loughran joined the SBP Graduate School of Biomedical Sciences in fall of 2018. He is in good academic standing. In 2020-2021 he will complete all coursework and then hold his Qualifying Exam.

The Sanford Burnham Prebys Medical Discovery Institute (SBP) Office of Education, Training & International Services (OETIS) oversees and coordinates an annual individual development planning (IDP) process for all postdocs at the Institute. The focus of the IDP process at SBP is the career goal of the postdoc; identification of what skills, knowledge, and accomplishments will be necessary for the postdoc to obtain a desired independent position following training; and identification of training and professional development opportunities that are available for the postdoc to obtain the necessary skills and knowledge. The SBP Office of Education, Training & International Services provides guidance and advising to both postdocs and PIs throughout the postdoc's training with respect to developing IDPs and preparing for a successful transition to independence post-training. The SBP Office of Education, Training & International Services also maintains webpages containing comprehensive resources on career path identification, career planning, and creating an IDP that can be utilized in conjunction with the formal annual IDP process.

The SBP IDP process includes two components:

1) **First-Year IDP (effective in 2014).** Within the first 3 months of beginning postdoctoral training at SBP, all postdocs receive and fill out an initial "planning and expectations" document to discuss with their PI. This document serves as the foundation for their postdoctoral IDP and is designed to facilitate discussion between the PI and new postdoc regarding goals and expectations for the first year of training, as well as stimulate initial discussions about long-term career goals and training plans.

2) **Postdoctoral IDP (effective January 2013).** At the end of the first year of training SBP postdocs receive notification that it is time to update their IDP, and they receive the information they included in their first-year planning and expectations document in the form of a full IDP that they can update with their accomplishments over the past year and their goals for the coming year, mid-term future, and long-term future. Each subsequent year of their postdoctoral training, postdocs will receive notification and the previous year's IDP form to update and expand. The IDP forms are designed to build upon each previous year as well as provide a solid foundation from which a postdoc can easily build his or her CV/resume.

During the past year I participated in Part 2 of the IDP process with Dr. Archna Ravi who started her postdoctoral training on 1/3/2017.

How were the results disseminated to communities of interest?
Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?
Unfortunately, this is the final report.

4. IMPACT

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

Nothing to Report.

What was the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

Nothing to Report.

5. CHANGES/PROBLEMS

Changes in approach and reasons for change.

Nothing to report.

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

Nothing to Report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to Report.

6. PRODUCTS

Publications, conference papers, and presentations.

Reviews

1. Palamiuc L, Ravi A, Emerling BM. Phosphoinositides in autophagy: current roles and future insights. FEBS J. 2020 Jan;287(2):222-238. doi: 10.1111/febs.15127. Epub 2019 Nov 21. Review. PubMed PMID: 31693781.
2. Renne MF, Emerling BM. ORP5 regulates PI(4)P on the lipid droplet: Novel players on the monolayer. J Cell Biol. 2020 Jan 6;219(1). doi: 10.1083/jcb.201912010. PubMed PMID: 31868890; PubMed Central PMCID: PMC7039197.

Presentations

1. Targeting Non-Canonical Phosphoinositide Signaling for Metabolic Homeostasis. Gordon Research Seminar: Molecular and Cellular Biology of Lipids, *Waterville Valley, New Hampshire (2019)*
2. Non-Canonical Phosphatidylinositol Kinases and Cellular Metabolism. Gordon Research Conference: Spatiotemporal Regulation of the Lipidome, *Waterville Valley, New Hampshire (2019)*
3. Targeting Non-Canonical Phosphoinositide Signaling for Metabolic Homeostasis. Inositol Lipids in Health and Diseases, 44th Symposium on Hormones and Cell Regulation, *Mont Sainte-Odile, France (2019)*
4. Metastatic Breast Cancer: A Research Viewpoint, Invited Lecture, Howell Foundation, *La Jolla, California (2019)*
5. Targeting Non-Canonical Phosphoinositide Signaling for Metabolic Homeostasis. Invited Lecture, Cedars-Sinai Cancer Center, *Los Angeles, California (2019)*
6. Targeting Non-Canonical Phosphoinositide Signaling for Metabolic Homeostasis. Invited Lecture, UCI Chao Family Comprehensive Cancer Center, *Irvine, California (2020)*
7. PI5P4Ks as drivers of metabolic rewiring in p53 mutant cancers, William Forbeck Scholar Symposium - Leveraging Synthetic Lethality to treat Cancer. *Rancho Santa Fe, California (2020)*

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?

The below information represents the participant efforts for the awarded period at SBP of 08/15/2019-05/31/2020.

Brooke Emerling (Principal Investigator) – 1.20 person months *(The total 1.20 calendar months' funding support was paid entirely by the grant and not supplemented from any discretionary or other funding source).*

Archna Ravi (Postdoctoral Associate) – 2.40 person months

Ryan Loughran (Graduate Student) – 12.00 person months

Elizabeth Daniele (Lab Manager) – 8.84 person months

Vivian Tieu (Research Assistant) – 5.05 person months *(Funding support was paid from Institute discretionary funds (start-up) from 04/01/2020 – 05/31/2020).*

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 attached.

What other organizations were involved as partners?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

Nothing to report.

9. APPENDICES

W81XWH-19-1-0614: Targeting the Non-Canonical Phosphoinositide Kinases in P53 Mutant Breast Cancer

PI: Brooke Emerling, Sanford Burnham Prebys Medical Discovery Institute, CA

Budget: $974,610

Topic Area: Breast Cancer Research Program **Mechanism:** Expansion Award

Research Area(s): Cancer Initiation (Oncogenes and Tumor Suppressor Genes); Normal Functioning
Award Status: 08/15/2019 – 05/31/2020

Study Goals:

The ultimate goal and the overall impact of this project are to characterize PI5P4Ks as a novel liability for breast tumors with TP53 mutations in order to define opportunities for therapeutic intervention for breast cancer patients with these mutations, which currently lack targeted therapy.

Specific Aims:

1) Determine the therapeutic potential of inhibiting the PI5P4Ks in mouse cancer models with p53 mutations.
2) Define the metabolic mechanisms underlying PI5P4K dependency in p53 mutant breast cancer cells.

Key Accomplishments and Outcomes:

Publications:

1) Palamiuc L, Ravi A, Emerling BM. Phosphoinositides in autophagy: current roles and future insights. FEBS J. 2020 Jan;287(2):222-238. doi: 10.1111/febs.15127. Epub 2019 Nov 21. Review. PubMed PMID: 31693781.
2) Renne MF, Emerling BM. ORP5 regulates PI(4)P on the lipid droplet: Novel players on the monolayer. J Cell Biol. 2020 Jan 6;219(1). doi: 10.1083/jcb.201912010. PubMed PMID: 31868890; PubMed Central PMCID: PMC7039197.

Patents: none to date

Funding Obtained:

1) 1 R01 CA237536-01A1 (NIH): Non-Canonical Phosphatidylinositol Kinases in Triple Negative Breast Cancer; $2,230,313 (total costs)

PREVIOUS/CURRENT/PENDING SUPPORT

EMERLING, Brooke M.

PREVIOUS

Title	Validation of CUB-Domain-Containing Protein 1 (CDCP1) as a Target for Protein Therapeutics
Grant #	Pfizer/CTI Program (Cantley)
Time Commitments	
Supporting Agency	Pfizer
Grants Officer	
Performance Period	06/20/14–03/31/16
Level of Funding	
Project Goals	The project goal was to develop monoclonal antibodies targeted against CDCP1 for treatment of cancers.
Overlap	None

Title	Targeting p53 Mutant HER2 Amplified Breast Cancers Through Inhibition of the Phosphatidylinositol-5-Phosphate 4-Kinases
Grant #	011-15.16 (PI: Emerling)
Time Commitments	0.6 calendar (5%)
Supporting Agency	The Mary Kay Foundation
Grants Officer	Michael Lunceford E-mail: Michael.Lunceford@mkcorp.com
Performance Period	08/01/2016–07/31/2017
Level of Funding	$57,639 (annual direct costs)
Project Goals	The goal of this project was to investigate the role of PI5P4K in HER2+ breast cancers.
Overlap	None

Title	The Role of the Phosphatidylinositol-5-Phosphate 4-Kinases in p53 Null Breast Cancers
Grant #	W81XWH-14-10440 (Emerling)
Time Commitments	8.52 calendar (71%)
Supporting Agency	Department of Defense
Grants Officer	Jamie A. Shortall E-Mail: jamie.a.shortall.civ@mail.mil
Performance Period	09/30/14–05/16/18
Level of Funding	$250,720 (annual direct costs)
Project Goals	The goal of this project was to investigate the role of the PI5P4Ks in the growth of p53 mutant breast cancers.
Overlap	None

Title	Targeting PI5P4K for Triple Negative Breast Cancer Therapy
Grant #	06-20-26 EMER (Emerling)
Time Commitments	1.8 calendar (15%)
Supporting Agency	American Association for Cancer Research
Grants Officer	Shannon M. Gallagher-Colombo, PhD grants@aacr.org
Performance Period	08/01/16–07/31/18
Level of Funding	$69,000 (annual direct costs)
Project Goals	The goal of this project is to provide proof-of-concept that targeting the PI5P4K enzymes would be an effective therapy for TP53 mutant breast cancers, especially the TNBC subgroup where targeted therapies have not been effective.
Overlap	None

Title	Targeting the Non-Canonical Phosphoinositide Kinases in P53 Mutant Breast Cancer
Grant #	W81XWH-19-19-1-0614 (Emerling)
Time Commitments	1.2 calendar (10%)
Supporting Agency	Department of Defense
Grants Officer	Jamie A. Shortall E-Mail: jamie.a.shortall.civ@mail.mil
Performance Period	08/15/2019-05/31/2020
Level of Funding	$166,6000 (annual direct costs)
Project Goals	Targeting the Non-Canonical Phosphoinositide Kinases in P53 Mutant Breast Cancer The scope of this study is to investigate the role of PI5P4K in the growth of p53 mutant breast cancers.
Overlap	None

Title	Cancer Center Support Grant (CCSG)
Grant #	5 P30 CA030199-38 (Powis)
Time Commitments	1.2 calendar (10%)
Supporting Agency	NIH/NCI
Grants Officer	Candace M. Cofie E-Mail: candace.cofie@nih.gov
Performance Period	07/29/2015-04/30/2020
Level of Funding	$1,993,563 (annual direct costs)
Project Goals	The Sanford Burnham Medical Research Institute's Cancer Center is dedicated to revealing the fundamental molecular causes of cancer and to applying this knowledge to the health of humans. Through continued commitment to collaborative and multidisciplinary research, our plans seek to propel our scientific activities onward to deliver results that will have a transformational impact in cancer research and medicine.
Overlap	None

CURRENT

Title	PI5P4K inhibitors/modulations project
Grant #	11469 (PI: M, Jackson)
Time Commitments	0.6 calendar (5%)
Supporting Agency	SBP's Translational Science Initiative, Prebys Center
Grants Officer	Samantha Daluz

	E-mail: sdaluz@sbpdiscovery.org
Performance Period	04/15/19–12/31/20
Level of Funding	$15,000 (annual direct costs)
Project Goals	To complete the PTS screen and associated follow-up and develop biochemical activity assays and CETSA assays for alpha and beta isoforms.
Overlap	None

Title	Non-Canonical Phosphatidylinositol Kinases in Triple Negative Breast Cancer
Grant #	1 R01 CA237536-0A1 (Emerling)
Time Commitments	2.4 calendar (20%)
Supporting Agency	NIH/NCI
Grants Officer	Candace M. Cofie candace.cofie@nih.gov
Performance Period	06/01/20–05/31/25
Level of Funding	$228,750 (annual direct costs)
Project Goals	The most frequently mutated gene in cancer is TP53; however, it has been difficult to directly target this gene with drugs. We have discovered that a distinct family of phosphatidylinositol kinases encoded by the genes PIP4K2A and PIP4K2B create a synthetic lethality when deleted in the context of TP53 mutant tissues in mice or in human breast cancer cell lines. This work will define how this liability can be exploited in order to identify opportunities for therapeutic intervention for patients with TP53 mutations, especially in triple negative breast cancer where targeted therapies have not been effective.
Overlap	None

Title	Cancer Center Support Grant (CCSG)
Grant #	5 P30 CA030199-39 (Powis)
Time Commitments	1.2 calendar (10%)
Supporting Agency	NIH/NCI
Grants Officer	Candace M. Cofie candace.cofie@nih.gov
Performance Period	05/29/20–04/30/25
Level of Funding	$2,093,241 (annual direct costs)
Project Goals	The mission of Sanford Burnham Prebys Medical Discovery Institute's Cancer Center is to be a national leader in the effort to overcome cancer as a cause of human suffering and death. Our vision is to make paradigm shifting discoveries that will underlie novel therapeutic modalities by creating, translating, and disseminating exceptional basic cancer science.
Overlap	None

Title	PI5P4Ks as drivers of metabolic rewiring in p53 mutant cancers
Grant #	RSG-20-064-01-TBE (Emerling)
Time Commitments	1.2 calendar (10%)
Supporting Agency	American Cancer Society
Grants Officer	Greta McShan E-Mail: Greta.mcshan@cancer.org
Performance Period	09/01/2020-08/31/2024
Level of Funding	$165,000 (annual direct costs)

Project Goals	The scope of this project is to dissect the distinct roles of the PI5P4Ks and their relationship with p53 in tumor metabolism, in the context of both loss of function and gain of function p53 mutations using novel endogenous tumor models.
Overlap	None

PENDING

None