AWARD NUMBER: W81XWH-19-1-0414

TITLE: Targeting tumor-specific apoptosis regulation in advanced ER+ breast cancer

PRINCIPAL INVESTIGATOR: Kris C. Wood

CONTRACTING ORGANIZATION: Duke University, Durham, NC

REPORT DATE: September 2021

TYPE OF REPORT: Annual Report

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

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
September 2021	Annual	15Aug2020-14Aug2021

4. TITLE AND SUBTITLE
Targeting tumor-specific apoptosis regulation in advanced ER+ breast cancer

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-19-1-0414

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Kris C. Wood, Ph.D.

E-Mail: kris.wood@duke.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Duke University
Dept of Pharm and Cancer Bio
2200 W. Main St.
Suite 820, Erwin Sq Plaza
Durham, NC 27705

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Development 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
Patients with advanced, ER+ breast cancer are commonly treated with combinations of anti-estrogen therapies plus CDK4/6 inhibitors. However, once they progress on this therapy, few proven treatment options remain. We recently made the surprising discovery that ER+ cell lines, xenografts, and patient tumors are highly "primed" to undergo apoptosis and specifically dependent on the anti-apoptotic BCL-2 family proteins BCL-X_L and MCL-1 for their survival. Direct, combined BCL-X_L/MCL-1 inhibition yields synergistic apoptosis induction in cell lines and regressions of tumors *in vivo*, an effect that can be phenocopied using combinations of BCL-X_L and mTOR inhibitors. The goal of this proposal is to build on the above discovery of a breast cancer-specific survival dependency by generating the key data necessary to motivate clinical trials exploring BCL-X_L plus mTOR inhibitors in patients who have progressed on anti-estrogen plus CDK4/6 inhibitor therapy. Specifically, we aim to evaluate the efficacy of combined BCL-X_L plus mTOR inhibition in "gold standard" mouse models, optimize the use of this combination therapy to sensitize tumors to low dose, cytotoxic chemotherapies and fulvestrant, and validate biomarkers that identify the patients most likely to respond to these treatments. Here, we describe key advances occurring during the second year of this award toward the realization of these goals.

15. SUBJECT TERMS
breast cancer, apoptosis, mTOR, BCL-XL, CDK4/6, ER, resistance

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	25	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

1. INTRODUCTION:

No proven, effective therapies exist for patients with estrogen receptor-positive (ER+) breast cancer following progression on standard of care anti-estrogen plus CDK4/6 inhibitor (AECi) therapy. We recently made the surprising discovery that breast cancer cell lines, xenografts, and patient tumors are highly "primed" to undergo apoptosis and specifically dependent on the anti-apoptotic BCL-2 family proteins BCL-X_L and MCL-1 for their survival (Anderson et al, *Science Translational Medicine* 2016, ra175). Direct, combined BCL-X_L/MCL-1 inhibition yields synergistic apoptosis induction in breast cancer cell lines and regressions of tumors *in vivo*, an effect that can be phenocopied using combinations of BCL-X_L and mTOR inhibitors in those tumors with *PIK3CA* activating mutations (which comprise over one-third of all ER+ cancers and one-half of those that progress on AECi therapy). The goal of this proposal is to build on the above discovery of a breast cancer-specific survival dependency by generating the key data necessary to evaluate the possibility of translating BCL-X_L plus mTOR inhibitor therapy in patients with ER+ disease who have progressed on AECi therapy. Specifically, we aim to evaluate the efficacy of combined BCL-X_L plus mTOR inhibition in "gold standard" patient-derived xenograft (PDX) mouse models of ER+ disease following progression on AECi therapy, optimize the use of this combination therapy to sensitize tumors to low dose, cytotoxic chemotherapies or fulvestrant, and validate biomarkers that identify the patients most likely to respond to these treatments. In this report, we summarize key advances occurring during the second year of this award toward the ultimate realization of these goals.

2. KEYWORDS: breast cancer, apoptosis, mTOR, BCL-X_L, CDK4/6, ER, resistance

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The major goals of this project are described in the approved Statement of Work associated with this funded proposal, which is copied in Table 1, below. In it, we list dates of actual completion relative to the projected timeline.

Aim 1: Evaluate the efficacy of mTORC1/2 + BCL-X_L inhibitor therapy in PDX models of advanced, ER+ breast cancer	**Timeline (months)**	**Date of actual completion**
Major Task 1: Establish PDX models of ER+, AECi resistant disease	1-9	12
Subtask 1: Establish tumor xenografts. A minimum of three orthotopic PDX models will be developed from patients with ER+ disease that has progressed on treatment with antiestrogens + palbociclib. n=6 mice	3-6	12
Subtask 2: Measure growth of xenografts through multiple passages to establish reliable growth characteristics of PDX models n=18 mice	6-9	12

Subtask 3: Develop primary cell lines from PDX models	6-9	12
Milestone(s) Achieved: Establishment of ER+, AECi resistant PDX models	9	12
Local IACUC/IRB Approval DoD HRPO/ACURO Approval	1-2 3	5 6
Milestone Achieved: IRB/IACUC/HRPO/ACURO Approval	3	6
Major Task 2: Evaluate preliminary mTORC1/2 + BCL-X_L inhibitor dose-response behavior in PDX models		
Subtask 1: Define dose-response behavior for mTORC1/2 + BCL-X_L inhibitors *in vivo* to define doses for subsequent studies n=221 mice	9-12	12
Subtask 2: Repeat as needed for determination of saturation dosing	9-12	12
Milestone(s) Achieved: Basic dose-response behavior established	12	12
Major Task 3: Evaluate the efficacy and tolerability of mTORC1/2 + BCL-X_L tumor targeting in PDX models		
Subtask 1: Evaluate mTORC1/2 + BCL-X_L *in vivo* in PDX models. Following orthotopic tumor development in each of the 3 PDX models, mice will be divided into 6 treatment groups: vehicle, MLN0128 only, navitoclax only, APG-1252 only, MLN0128 + navitoclax, and MLN0128 + APG-1252. n=360 mice	12-15	20
Subtask 2: Perform immunostaining of treated tumors to examine markers of growth, apoptosis, and mTOR/BCL-X_L target inhibition following drug treatments	14-15	In progress
Milestone(s) Achieved: Efficacy and tolerability of mTORC1/2 + BCL-X_L determined *in vivo*; BCL-X_L inhibitor for future studies selected	15	20
Aim 2: Evaluate mechanism-based synergy between low dose mTORC1/2 + BCL-X_L inhibition and standard-of-care chemotherapies and ER targeted therapies	**Timeline (months)**	**Date of actual completion**
Major Task 1: Define synergistic combinations of cytotoxic chemotherapies plus mTORC1/2-BCL-X_L inhibitors in cellular models of ER+ disease Cell lines: MCF7 derivatives with in vivo acquired resistance to antiestrogen + CDK4/6i (derived in-house); primary lines derived from Aim 1 PDX models using conditional reprogramming (derived	**1-6**	**9**

in-house)		
Subtask 1: Determine impact of cytotoxic chemotherapies (docetaxel, carboplatin, and doxorubicin)/fulvestrant plus mTORC1/2-BCL-X_L inhibitors on proliferation in ER+ models	1-6	10
Subtask 2: Determine impact of cytotoxic chemotherapies/ fulvestrant plus mTORC1/2-BCL-X_L inhibitors on apoptosis in ER+ models	1-6	12
Milestone(s) Achieved: Define optimal chemotherapy/ fulvestrant plus mTORC1/2-BCL-X_L inhibitor combinations in cellular ER+ models	6	12
Local IACUC Approval DoD ACURO Approval	12-13 14	5 6
Milestone Achieved: IACUC/ACURO Approval	14	6
Major Task 2: Define the mechanism(s) of apoptotic priming by high priority chemotherapies or fulvestrant Cell lines: See above (Aim 2, Major Task 2)	6-15	20
Subtask 1: Perform BH3 profiling and immunoblotting in presence and absence of chosen chemotherapies/fulvestrant to define impact of chosen agents on apoptotic priming	6-9	12
Subtask 2: Rescue apoptotic priming through functional complementation experiments to confirm mechanisms of priming	9-15	20
Milestone(s) Achieved: Identification of mechanisms of apoptotic priming by high priority chemotherapies	15	20
Major Task 3: Evaluate chemotherapeutic sensitization using low doses of mTORC1/2-BCL-X_L inhibitors in vivo	15-24	22
Subtask 1: Evaluate synergy between chemotherapies/fulvestrant and low dose mTORC1/2 + BCL-X_L inhibitors *in vivo* in PDX models n=220 mice	15-22	22
Subtask 2: Perform immunostaining of treated tumors to examine markers of growth, apoptosis, and mTOR/BCL-X_L target inhibition following drug treatments	22-24	In progress
Milestone(s) Achieved: Efficacy and tolerability of chemotherapy plus low dose mTORC1/2 + BCL-X_L inhibitors determined *in vivo*	24	22

Aim 3: Define the major determinants of response to mTORC1/2 + BCL-X_L inhibition in ER+ tumors	**Timeline (months)**	**Date of actual completion**
Major Task 1: Characterize the spectrum of cellular responses to combined mTORC1/2-BCL-X_L inhibition in ER+ models Cell lines: MCF7 derivatives with in vivo acquired resistance to antiestrogen + CDK4/6i (derived in-house); primary ER+ lines derived from PDX models using conditional reprogramming (derived in-house)	24-30	
Subtask 1: Perform WES, RNA-seq, growth and apoptosis assays in multiple ER+ cell lines to capture cell line diversity	24-28	
Subtask 2: Analyze response determinants to identify candidate modifiers of response	24-30	
Subtask 3: Functionally validate leading candidates using stable lentiviral cDNA or CRISPR/Cas9 systems as appropriate	27-30	
Milestone(s) Achieved: Characterization of the spectrum of drug sensitivities across ER+ lines and primary cultures	30	
Local IRB Approval DoD HRPO Approval	22-23 24	
Milestone Achieved: IRB/HRPO Approval	24	
Major Task 2: Define the relationship between the integrity of the mitochondrial apoptosis circuitry and sensitivity to mTORC1/2-BCL-X_L inhibition	28-36	
Subtask 1: Perform BH3 profiling and immunoblotting to define mechanisms of insensitivity to mTORC1/2-BCL-X_L inhibitor combinations	28-32	
Subtask 2: Rescue mTORC1/2-BCL-X_L inhibitor sensitivity through functional complementation experiments to confirm mechanisms of resistance	32-36	
Milestone(s) Achieved: Definition of the mechanisms of intrinsic resistance to mTORC1/2-BCL-X_L inhibitor combinations	36	
Major Task 3: Evaluate sensitivity correlates in patients enrolled in a Phase 1 clinical trial testing the combination of MLN0128 plus either navitoclax or APG-1252.	24-36	
Subtask 1: Obtain FFPE samples of tumors at baseline, on treatment (1 week), and on progression, and perform staining and sequencing assays	26-30	

Subtask 2: Quantify positive/negative staining of patient samples and differential mutation or gene expression signatures associated with response	30-36	
Milestone(s) Achieved: Assessment of target inhibition and preliminary relationships between the key molecular mediators of response and clinical activity in patients	36	
Local IRB Approval DoD HRPO Approval	24-25 26	

Table 1: Statement of Work (SoW).

What was accomplished under these goals?

1. Major activities

During the second reporting period, our activities focused on the following key areas, all of which are in line with our original, stated goals and project plans (Table 1):

(i) Selecting a BCL-X_L inhibitor for our ongoing and future *in vivo* studies
(ii) Defining the efficacy and tolerability of mTORC1/2 + BCL-X_L inhibitors in models of ER+ breast cancer *in vivo*
(iii) Identifying mechanisms of apoptotic priming by high priority chemotherapies
(iv) Defining the efficacy and tolerability of chemotherapy plus mTORC1/2 + BCL-X_L inhibitors in models of ER+ breast cancer *in vivo*

2. Specific Objectives

The Specific Objectives for the second reporting period, listed in Table 1 above, were:

(i) To evaluate the efficacy and tolerability of mTORC1/2 + BCL-X_L tumor targeting in PDX models of ER+ breast cancer, using one of two possible BCL-X_L inhibitor candidates, with associated immunohistochemical analysis of tumor specimens from treated mice **(Aim 1, Major Task 3)**
(ii) To rescue apoptotic priming through functional complementation experiments to confirm mechanisms of priming **(Aim 2, Major Task 2)**
(iii) To evaluate chemotherapeutic sensitization using mTORC1/2-BCL-X_L inhibitors in PDX models of ER+ breast cancer, with associated immunohistochemical analysis of tumor specimens from treated mice **(Aim 2, Major Task 3)**.

3. Significant results

(i) To evaluate the efficacy and tolerability of mTORC1/2 + BCL-X_L tumor targeting in PDX models of ER+ breast cancer, using one of two possible BCL-X_L inhibitor candidates, with associated immunohistochemical analysis of tumor specimens from treated mice **(Aim 1, Major Task 3)**

During the first year of our project, we set the stage for the work in year 2 under Aim 1, Major Task 3 by defining safe and effective doses of combined mTOR and BCL-X_L inhibitors (MLN0128 and ABT737/APG-1252, respectively). Then, using the data from these studies, we selected one of the two BCL-X_L inhibitors (ABT737 or APG-1252) for all subsequent studies. We established that doses of 25 mg/kg daily and 0.3 mg/kg daily of ABT-737 and MLN0128, respectively, which have previously been demonstrated to yield on-target inhibition *in vivo* (Anderson et al, *Science Translational Medicine* 2016, **8**, 369ra175), exhibited synergistic efficacy without evidence of toxicity in xenograft models of ER+ breast cancer (MCF7; Figure 1). Further, we demonstrated that 25 mg/kg daily doses of APG-1252, which were suggested to us as yielding on-target inhibition of BCL-X_L by the drug's manufacturer, could be safely administered in combination with MLN0128 (dose above) without evidence of toxicity (Figure 1). Finally, we observed that ABT-737 behaved in a manner consistent with our prior studies; namely, it yielded little anti-tumor activity as a single agent *in vivo* (consistent with our prior observation, cited above, that diverse BCL-X_L inhibitors yield low activity in breast cancer models when used alone) while yielding highly synergistic activity in combination with MLN0128. By contrast, APG-1252 yielded substantial single agent activity *in vivo* without evidence of synergistic activity in combination of MLN0128 (Figure 1). These findings led us to select ABT-737 (navitoclax) for all subsequent *in vivo* studies.

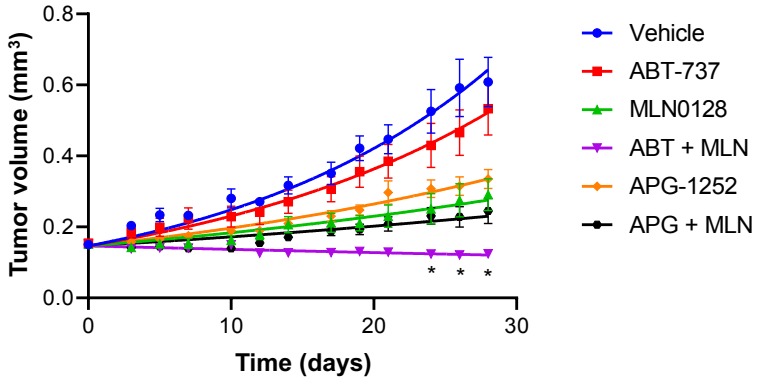

Figure 1: Growth of models of ER+ breast cancer treated with the mTORC1/2 inhibitor MLN0128, the BCL-X_L/BCL-2 inhibitor ABT-737, the BCL-X_L/BCL-2 inhibitor APG-1252, or the indicated combinations. Six mice per group. *p < 0.05.

Having selected the combination of MLN0128 + ABT-737 for all subsequent PDX models of ER+ disease in this project, we proceeded to characterize this combination in the PDX models HCI-003, HCI-011, and HCI-017, which were described in our previous progress report. As shown in Figure 2a (left), we observed evidence of impressive synergistic activity in the HCI-003 model. However, our ability to assess the antitumor activity of this combination therapy was blunted by toxicity, as indicated by declining body weights in treated mice (Figure 2a, right), which was greater in the NOD-SCID mice used for PDX studies than was observed in the nude mice used for our preliminary studies. For this reason, the study had to be terminated after 21d of drug treatment. In the HCI-011 model, we observed early indications of tumor growth control, but it was impossible to resolve the relative impacts of the single agents versus the combination therapy because of the study's short timeframe, which was forced by toxicity (Figure 2b). The final PDX model, HCI-017, grew too slowly to perform xenograft studies in year 2 and remains under consideration for study in year 3. Together, by evaluating mTOR + BCL-X_L inhibition in PDX models of ER+ breast cancer, and demonstrating that this strategy yields synergistic antitumor activity in one such model, these studies have achieved the major objectives of Aim 1,

Major Task 3. We note that immunohistochemical staining of the tumors recovered from treated mice is ongoing at this time.

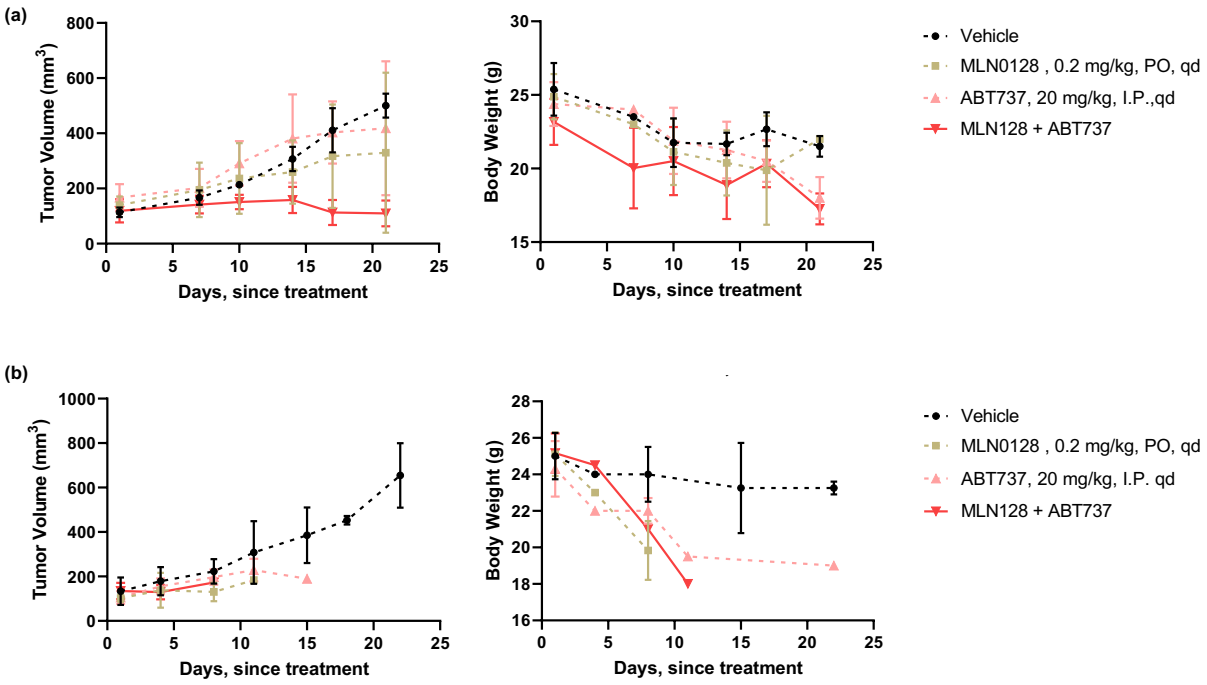

Figure 2: PDX models of ER+ breast cancer treated with the mTORC1/2 inhibitor MLN0128 and the BCL-X_L/BCL-2 inhibitor ABT-737. (a) HCI-003, with tumor volume at left and mouse weight at right. (b) HCI-011, with tumor volume at left and mouse weight at right.

(ii) To rescue apoptotic priming through functional complementation experiments to confirm mechanisms of priming **(Aim 2, Major Task 2)**

The purpose of the studies in Aim 2, Major Task 2 is to define the determinants of apoptotic priming by chosen chemotherapeutics in ER+ breast cancer. In ER+ breast cancer cells with *in vivo* acquired resistance to AECi therapy, we observed during year 1 incomplete loss of the anti-apoptotic proteins BCL-2 and BCL-X_L following treatment with doxorubicin and etoposide, respectively, when used in combination with mTOR + BCL-X_L inhibition. These studies, which comprise subtask 1, suggest that these effects may explain the increased apoptotic activity of the combination therapies. In year 2, our studies in subtask 2 evaluated the functional roles of these proteins in apoptotic commitment following combination therapy treatments, as described in our Statement of Work. Specifically, we overexpressed BCL-2 or BCL-X_L, then assessed their impacts on PARP cleavage (Figure 3) and cellular survival (Figure 4), in both cases revealing partial rescues of drug-induced apoptosis. Consistent with this, we also found that knockout of BIM, a BH3-only member of the BCL-2 family of proteins that directly opposes the functions of BCL-2 and BCL-X_L, by each of two sgRNAs (via CRISPR/Cas9) was sufficient to partially rescue drug-induced PARP cleavage (Figure 5) and cell death (Figure 6). Together, these data indicate that BCL-2/BCL-X_L suppression contributes to the mechanism of cell death induced by combinations of chemotherapeutics and mTORC1/2-BCL-X_L inhibitors, thus achieving the major objectives of Aim 2, Major Task 2.

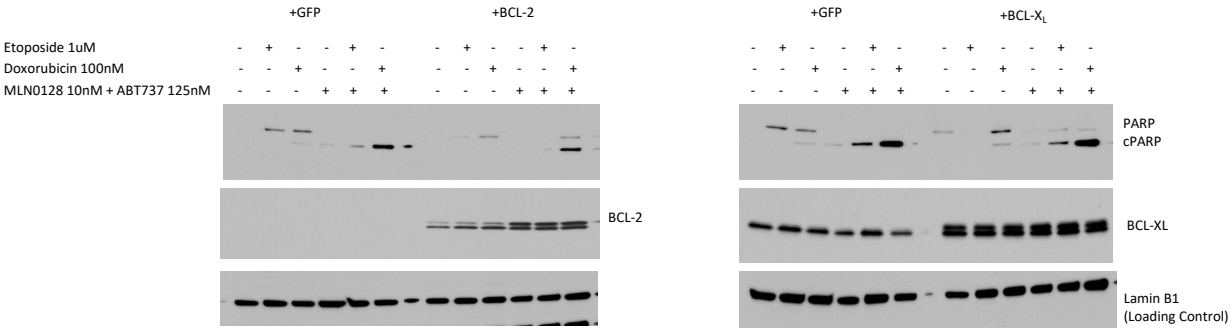

Figure 3: Effect of indicated drugs on PARP cleavage in cells harboring or lacking the overexpression of BCL-2 or BCL-X$_L$.

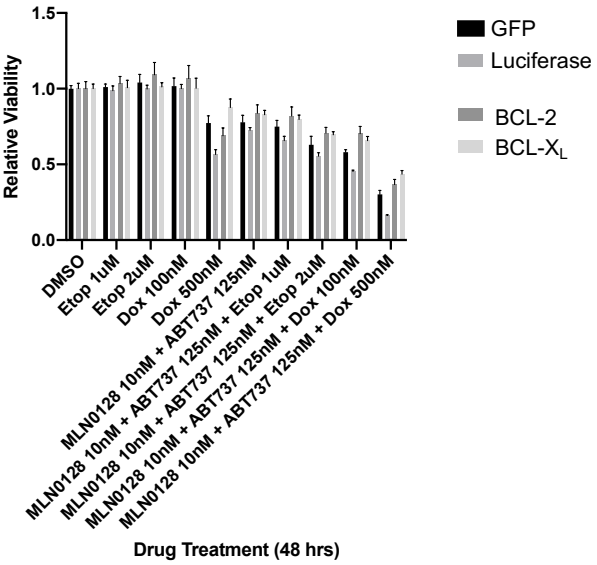

Figure 4: Effect of indicated drugs on the survival of cells harboring or lacking the overexpression of BCL-2 or BCL-X$_L$.

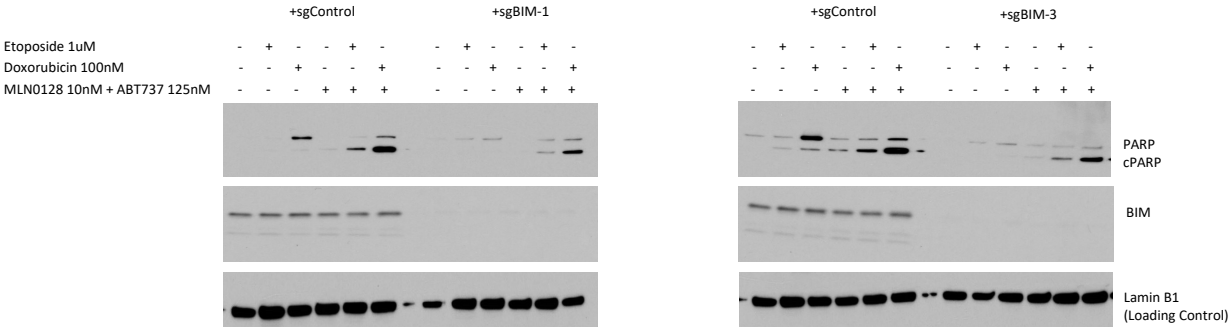

Figure 5: Effect of indicated drugs on PARP cleavage in cells harboring or lacking BIM.

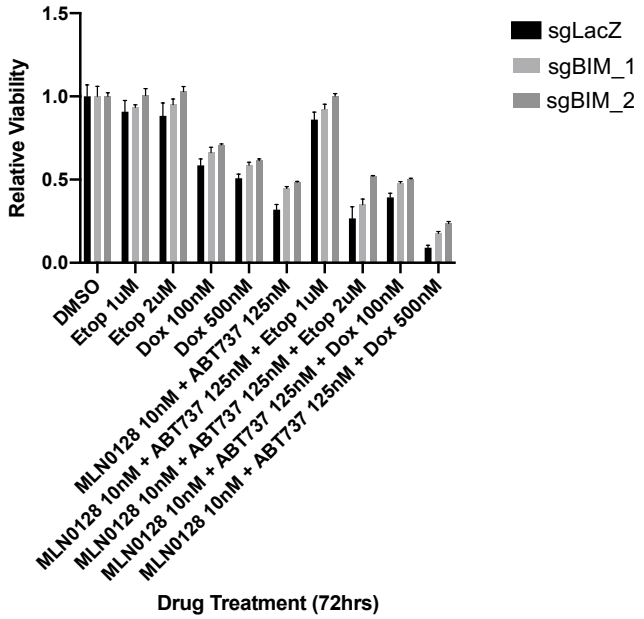

Figure 6: Effect of indicated drugs on the survival of cells harboring or lacking BIM.

(iii) To evaluate chemotherapeutic sensitization using mTORC1/2-BCL-X_L inhibitors in PDX models of ER+ breast cancer, with associated immunohistochemical analysis of tumor specimens from treated mice **(Aim 2, Major Task 3)**.

Our preliminary data and studies in Year 1 demonstrated that combined mTORC1/2-BCL-X_L inhibition can lower the apoptotic threshold in breast cancer cells, sensitizing them to subsequent chemotherapy treatment. Based on these findings, we proposed in Aim 2, Major Task 3 to evaluate the response to the triple drug combination of the mTORC1/2 inhibitor MLN0128, the BCL-2/BCL-X_L inhibitor ABT-737, and the anthracycline chemotherapeutic doxorubicin. Performing these studies in the HCI-003 and HCI-011 models, we unfortunately observed a rapid induction of toxicity in the triple therapy-treated mice, forcing us to halt these studies before conclusive results could be obtained (Figure 7). The observation the triple drug therapy exhibits substantially increased toxicity relative to mTORC1/2-BCL-X_L inhibition alone suggests that this triple therapy approach is less viable than the dual therapy approach consisting of mTORC1/2-BCL-X_L inhibition alone. While ongoing and future studies may further evaluate this triple therapy concept using lower doses of each drug, or alternative cytotoxic chemotherapies, these existing studies have achieved the major objectives of Aim 2, Major Task 3. We note that immunohistochemical staining of the tumors recovered from treated mice is ongoing at this time.

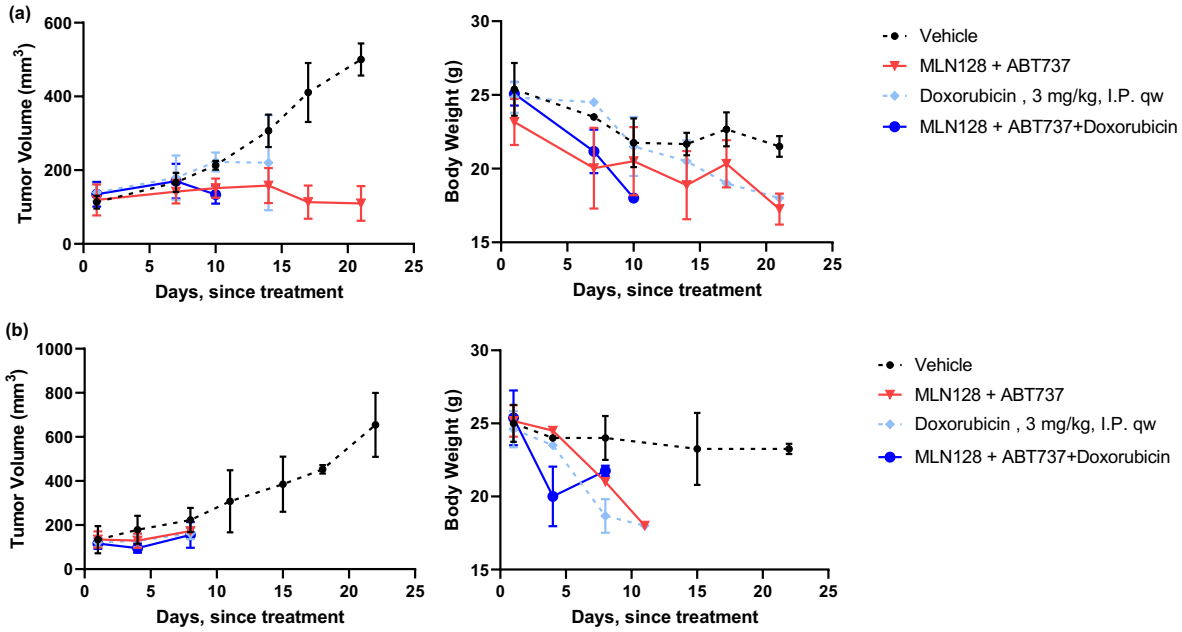

Figure 7: PDX models of ER+ breast cancer treated with the mTORC1/2 inhibitor MLN0128 and the BCL-X_L/BCL-2 inhibitor ABT-737, with or without doxorubicin. (a) HCI-003, with tumor volume at left and mouse weight at right. (b) HCI-011, with tumor volume at left and mouse weight at right. Doses of MLN0128 and ABT-737 are as in Figure 2.

Stated goals not met

We have not yet completed the immunostaining of tumors treated with BCL-X_L inhibitors, mTORC1/2 inhibitors, and/or doxorubicin as described in **Aim 1, Major Task 3, Subtask 2** and **Aim 2, Major Task 3, Subtask 2**. These studies are in progress at this time.

4. Other achievements

No publications have resulted from this work to date.

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

With respect to training, each of the individuals who worked on and derived support from this project over its second year met weekly with the PI, Dr. Wood, to discuss progress and challenges, and to plan next experiments. These include individuals paid directly from the grant as well as graduate students who also worked on the project but are funded by training fellowships. These weekly one-on-one sessions provided each of these scientists with individualized, detailed instruction on topics ranging from laboratory experiments and data analysis to career development.

With respect to professional development, each of the above scientists also participated in the Duke University Department of Pharmacology and Cancer Biology's scientific retreat, held virtually in September. This two-day retreat included virtual podium and poster presentations as well as professional development and networking sessions. Further, each of the trainees listed above also participated in the Department's virtual weekly seminar series, where experts in cancer biology and signaling from around the world come to Duke to present their latest

findings. (We note that in 2020-21, these activities were held virtually due to COVID-19-related meeting restrictions.)

How were the results disseminated to communities of interest?

Our DoD-funded studies were described at the 2019 Duke Cancer Institute Fall Shingleton Society Luncheon, a gathering of supporters and donors who are local champions of cancer research. Dr. Wood was the keynote speaker at this event. They were also described at the V Foundation for Cancer Research's V Scholar Summit in 2021, where Dr. Wood was one of three guest speakers.

What do you plan to do during the next reporting period to accomplish the goals?

Our major efforts during the coming reporting period are focused on (1) completing the immunohistochemical staining of tumors from Aims 1-2 (described above); (2) characterizing the spectrum of cellular responses to combined mTORC1/2-BCL-X_L inhibition in ER+ models (Aim 3, Major Task 1); (3) defining the relationship between the integrity of the mitochondrial apoptosis circuitry and sensitivity to mTORC1/2-BCL-X_L inhibition (Aim 3, Major Task 2); and (4) evaluating sensitivity correlates in patients enrolled in a Phase 1 clinical trial testing the combination of MLN0128 plus either navitoclax or APG-1252 (Aim 3, Major Task 3).

IMPACT:

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

This work has impacted the field of breast cancer research by discovering, for the first time, that breast cancer cells are highly primed for apoptosis and specifically dependent upon the anti-apoptotic proteins BCL-X_L and MCL-1 for their survival. Further, by showing that this apoptotic dependency can be pharmacologically exploited using combination therapies consisting of BCL-X_L inhibitors and mTOR inhibitors, with or without low dose cytotoxic chemotherapies, this work has defined a clinically translatable path for exploiting this discovery for the potential benefit of women with ER+ disease who progress on AECi therapy. Our ongoing studies will define the clinical potential and path forward for this therapeutic strategy using preclinical models and patient samples.

What was the impact on other disciplines?

The discovery that breast cancer cells are highly primed for apoptosis and specifically dependent upon the anti-apoptotic proteins BCL-X_L and MCL-1 for their survival suggests that other cancers may also harbor similar, exploitable apoptotic survival dependencies. In fact, our recent work revealed that the sensitivity of breast cancers to inhibitors of BCL-X_L and MCL-1 is not entirely a unique feature of breast cancer cells, and instead that many other solid tumors exhibit a similar vulnerability (Soderquist et al, *Nature Communications* 2018, **9**, 3513).

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

The ultimate goal of this project is to leverage our discovery that breast cancer cells are highly primed for apoptosis and specifically dependent upon the anti-apoptotic proteins BCL-X_L and MCL-1 for their survival to create combination therapies that are translated to human patients. Based on these and related findings, we are now working to initiate a clinical trial to evaluate these therapies in ER+ breast cancer patients at Duke University.

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. See above for project summary.

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

Nothing to report. All activities under these headings have been reviewed and approved by both the relevant Duke University and DoD parties.

PRODUCTS:

Publications, conference papers, and presentations

Journal publications.

Nothing to report.

Books or other non-periodical, one-time publications. Nothing to report.

Other publications, conference papers, and presentations.

Presentations citing support from this award (all by the PI, K.C.W.)

1. 2019, NCI Physical Sciences-Oncology Network (PS-ON) and Cancer Systems Biology Consortium (CSBC) Annual Junior Investigators' Meeting (Keynote lecturer)
   Invited by the organizing committee
2. 2019, Cold Spring Harbor Laboratory Meeting: Cell Death, Cold Spring Harbor, NY.
   Invited by the organizing committee
3. 2020, Quantitative Biology of the Cancer Cell Symposium, San Francisco, CA
   UCSF/UCSD Cancer Cell Mapping Initiative
   Invited by Sourav Bandyopadhyay, Ph.D. and Davide Ruggero, Ph.D.
4. 2020, Sixth AACR-IASLC International Joint Conference: Lung Cancer Translational Science from the Bench to the Clinic, San Diego, CA.
   Invited by conference organizers: Christine Lovly, M.D./Ph.D. and Trever Bivona, M.D./Ph.D.
5. 2020, LabRoots 8th Annual Genetics Virtual Week, Precision Medicine Symposium
   Invited by the organizers
6. 2020, St. Jude Children's Research Hospital, Dept. of Cell and Molecular Biology, Memphis, TN (virtual)
   Invited by Paul Taylor, M.D., Ph.D.
7. 2020, Dana-Farber / Harvard Cancer Center (DFHCC) Connect:Science Virtual Seminar Series (virtual)
   Invited by Kris Sarosiek, Ph.D.
8. 2020, Virtually Dead Episode I: Mitochondria Symposium (virtual)
   Invited by Stephen Tait, Ph.D. and Ana Garcia Saez, Ph.D.
9. 2021, Peter MacCallum Cancer Centre, Melbourne, Australia (virtual)
   Invited by Lev Kats, Ph.D.
10. 2021, Syros Pharmaceuticals (virtual)
    Invited by Susan Henry, Ph.D.
11. 2021, V Scholar Summit, Speaker and panelist, SAS Institute, Raleigh, NC (virtual)
    Invited by the organizers
12. 2021, AACR Annual Meeting, Session on Therapy Resistance in Leukemia (virtual)
    Invited by Catherine Wu, M.D.
13. 2021, Vanderbilt University, Dept. of Pathology, Microbiology, and Immunology (virtual)
    Invited by the graduate students
14. 2021, LabRoots CRISPR 2021 (virtual)
    Invited by the organizers
15. 2021, Vividion Therapeutics
    Invited by Robert Abraham, Ph.D.

Website(s) or other Internet site(s)

Wood lab website: https://sites.duke.edu/woodlab/

Technologies or techniques

Nothing to report.

Inventions, patent applications, and/or licenses

Nothing to report.

Other Products

Nothing to report.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Year 1:

Name:	*Kris Wood, Ph.D.*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	*Orcid.org/0000-0002-5887-2253*
Nearest person month worked:	*2*
Contribution to Project:	*Dr. Wood supervised all aspects of the work, meeting weekly with trainees to ensure that the goals of the project were met.*
Funding Support:	*This award*

Name:	*Min Lu, Ph.D.*
Project Role:	*Research Analyst*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*2*
Contribution to Project:	*Dr. Lu led the animal studies presented in this report.*
Funding Support:	*This award*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

There have been changes in the active support of the PI, Dr. Wood, which are summarized below:

Grants that expired during the last reporting period (annual direct costs to the Wood lab are indicated):

(Wood) 2/1/19-1/31/21 2.40 calendar months
Ovarian Cancer Research Alliance
Selective targeting of mitochondrial alterations in ovarian cancer
The major goal of this project is to define strategies for targeting altered mitochondrial dynamics in ovarian cancer.

N/A (Wood) 5/6/19-5/5/21 0.00 calendar months
Silicon Valley Community Foundation
Defining the genomic determinants of response to a first-in-class selective inhibitor of ATM and DNA-PK
The major goal of this project is to define genomic determinants of sensitivity to dual ATM/DNA-PK inhibition in cancer.
Effort not required

(Wood) 2/1/20-7/31/21 .12 calendar months
Tavros Therapeutics
Evaluating small molecules that potentiate anti-tumor immunity
This project is devoted to evaluating the immunogenic activity of small molecules that regulate cell death.

Grants that were newly funded during the last reporting period (annual direct costs to the Wood lab are indicated):

W81XWH-21-1-0362 (Wood) 6/1/21-5/31/23 1.20 calendar months DoD LCRP
Exploiting targeted therapy-induced ATM dependence in residual lung tumors
The major goals of this project are to define mechanism-based therapeutic strategies to eradicate residual disease in oncogene-driven lung cancers.

What other organizations were involved as partners?
Nothing to report.

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: N/A.

QUAD CHARTS: N/A.

APPENDICES:
(1) Copy of the PI's current CV

Last updated: 9/3/2021

Curriculum Vitae

Kris C. Wood
Associate Professor of Pharmacology and Cancer Biology
Duke University

CONTACT INFORMATION

450 Research Drive
C259 LSRC, DUMC 3813
Durham, NC 27710

Phone:
kris.wood@duke.edu

EDUCATION AND TRAINING

6/07-7/12 NIH Postdoctoral Fellow, Whitehead Institute for Biomedical Research, Cambridge, MA
Broad Institute of Harvard and MIT and Howard Hughes Medical Institute
Advisor: David M. Sabatini, M.D., Ph.D.

9/02-5/07 Ph.D., Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA
Advisors: Paula T. Hammond, Ph.D. and Robert S. Langer, Sc.D.
Minor: Cell Biology

8/98-5/02 B.S., Chemical Engineering, University of Kentucky, Lexington, KY
Summa Cum Laude (GPA: 4.0/4.0, Class Rank: 1/30)

PROFESSIONAL EXPERIENCE

8/12-Present Duke University, Durham, NC
Associate Professor with tenure (2020-Present)
Assistant Professor (2012-20)
Department of Pharmacology and Cancer Biology, School of Medicine (primary)
Department of Biomedical Engineering, Pratt School of Engineering (secondary)
Graduate program memberships: Molecular Cancer Biology, Pharmacology, Medical Scientist Training Program, Cell and Molecular Biology, University Program in Genetics and Genomics, Computational Biology and Bioinformatics, Biomedical Engineering

6/01-9/01 Massachusetts Institute of Technology, Cambridge, MA
NSF Summer Undergraduate Research Fellow, Center for Materials Science and Engineering

5/00-5/01; University of Kentucky, Lexington, KY
9/01-5/02 NSF Undergraduate Research Fellow, Department of Chemical Engineering

SCHOLARSHIPS, FELLOWSHIPS, HONORS, AND PROFESSIONAL SERVICE

2020-Present Associate Editor, *npg Precision Oncology*
2016-2019 Breakthrough Award, DoD Breast Cancer Research Program
2016-2017 Member, Board of Associate Scientific Advisors, *Science Translational Medicine*
2015-2018 Liz Tilberis Early Career Award, Ovarian Cancer Research Fund
2013-2015 V Scholar Award, V Foundation for Cancer Research
2013-2015 Stewart Trust Fellowship
2013-2017 Forbeck Scholar Award
2013-2015 Lloyd Trust Translational Research Award
2013-2014 Golfers Against Cancer Research Award
2013-2016 Whitehead Scholar Award

2012-2014	BIRCWH Scholar Award
2011-2012	Misrock Fund Postdoctoral Fellowship in Cancer Research
2008-2011	NIH Ruth L. Kirschstein National Research Service Award (F32)
2008-2011	American Cancer Society Postdoctoral Fellowship (declined)
2006-2007	Ludwig Graduate Fellowship in Molecular Oncology
2006	Materials Research Society Graduate Student Silver Award
2006	Outstanding Seminar Award, Chemical Engineering, MIT (Spring)
2002-2003	DuPont-MIT Fellowship
2002	University of Kentucky (UK) College of Engineering Tau Beta Pi Outstanding Senior Award
2002	UK Omega Chi Epsilon Outstanding Senior in Chemical Engineering Award
2001-2002	Barry M. Goldwater Scholarship for Science and Mathematics
2001	UK AIChE Outstanding Junior in Chemical Engineering Award
2000	UK AIChE Donald F. Othmer Sophomore Academic Excellence Award
1998	UK General Chemistry Award

PUBLICATIONS (* denotes corresponding author(s))

Original research

1. Meyer, D.E.; **Wood, K.**; Bachas, L.G.; Bhattacharyya, D.* (2004). Degradation of chlorinated organics by membrane-immobilized nanosized metals, *Environ. Prog.*, **23**, 232-242.
2. **Wood, K.C.**; Boedicker, J.Q.; Lynn, D.M.; Hammond, P.T.* (2005). Tunable drug release from hydrolytically degradable layer-by-layer thin films, *Langmuir*, **21**, 1603-1609.
3. **Wood, K.C.**; Little, S.R.; Langer R.*; Hammond, P.T.* (2005). A family of hierarchically self-assembling linear-dendritic hybrid polymers for targeted efficient gene delivery, *Angew. Chem. Int. Ed.* **44**, 6704-6708.
4. **Wood, K.C.**; Chuang, H.F.; Batten, R.D.; Lynn, D.M.; Hammond, P.T.* (2006). Controlling interlayer diffusion to achieve sustained, multi-agent drug delivery from layer-by-layer thin films," *Proc. Natl. Acad. Sci. USA* **103**, 10207-10212.
5. **Wood, K.C.**; Zacharia, N.S.; Schmidt, D.J.; Wrightman, S.; Andaya, B.J.; Hammond, P.T.* (2008). Electroactive controlled release thin films, *Proc. Natl. Acad. Sci. USA* **105**, 2280-2285.
6. **Wood, K.C.**; Azarin, S.M.; Arap, W.; Pasqualini, R.; Langer, R.*; Hammond, P.T.* (2008). Tumor-targeted gene delivery using molecularly engineered hybrid polymers functionalized with a tumor-homing peptide, *Bioconjugate Chem.* **19**, 403-405.
7. **Wood, K.C.***; Konieczkowski, D.J.; Johannessen, C.M.; Boehm, J.S.; Tamayo, P.; Botvinnik, O.B.; Mesirov, J.P.; Hahn, W.C.; Root, D.E.; Garraway, L.A.; Sabatini, D.M.* (2012). MicroSCALE screening reveals genetic modifiers of therapeutic response in melanoma, *Science Signaling* **5**, rs4.
8. Wood, K.B.; **Wood, K.C.**; Nishida, S.; Cluzel, P.* (2014). Conservation laws for resistance to multi-drug treatments in microbes and human cancer cells, *Cell Reports* **6**, 1073.
9. Martz, C.A.[¶]; Ottina, K.A.[¶]; Singleton, K.S.[¶]; Jasper, J.S.; Wardell, S.E.; Peraza-Penton, A.; Anderson, G.R.; Winter, P.S.; Wang, T.; Alley, H.M.; Kwong, L.N.; Cooper, Z.A.; Tetzlaff, M.; Chen, P.-L.; Rathmell, J.C.; Flaherty, K.T.; Wargo, J.A.; McDonnell, D.M.; Sabatini, D.M.*; **Wood, K.C.*** (2014). Systematic identification of signaling pathways with potential to confer anticancer drug resistance, *Science Signaling* **7**, ra121. ([¶]Co-first authors)
10. Winter, P.S.; Sarosiek, K.A.; Lin, K.H.; Meggendorfer, M.; Schnittger, S.; Letai, A.; **Wood, K.C.*** (2014). RAS signaling promotes resistance to JAK inhibitors by suppressing BAD-mediated apoptosis, *Science Signaling* **7**, ra122.
11. Gerriets, V.A.; Kishton, R.J.; Nichols, A.G.; Macintyre, A.N.; Inoue, M.; Ilkayeva, O.; Winter, P.S.; **Wood, K.C.**; Liu, X.; Priyadharshini, B.; Slawinska, M.E.; Haeberli, L.; Huck, C.; Turka, L.A.; Hale, L.P.; Smith, P.A.; Schneider, M.A.; MacIver, N.J.; Locasale, J.W.; Newgard, C.B.; Shinohara, M.L.; Rathmell, J.C.*

(2014). Metabolic Programming and PDHK1 Control CD4 T-Cell Subsets and Inflammation, *J. Clin. Inv*. **125**(1):194-207.

12. Misale, S.[¶]; Bozic, I.[¶]; Tong, J.; Peraza-Penton, A.; Lallo, A.; Baldi, F.; Lin, K.H.; Truini, M.; Trusolino, L.; Bertotti, A.; Di Nicolantonio, F.; Nowak, M.A.; Zhang, L.; **Wood, K.C.**; Bardelli, A.* (2015). Vertical suppression of the EGFR pathway delays onset of resistance in colorectal cancer models, *Nature Communications* **6**,8305-14. ([¶]Co-first authors)

13. Son, S.; Stevens, M.M.; Chao, H.X.; Thoreen, C.; Hosios, A.M.; Schweitzer, L.D.; Weng, Y.; **Wood, K.**; Sabatini, D.; Vander Heiden, M.G.; Manalis, S.* (2015). Cooperative nutrient accumulation sustains growth of mammalian cells, *Sci. Rep*. **5**, 17401.

14. Park, S.; Chang, C.; Safi, R.; Liu, X.; Baldi, R.; Jasper, J.; Anderson, G.; Liu, T.; Rathmell, J.; Dewhirst, M.W.; **Wood, K.C.**; Locasale, J.W.; McDonnell, D.P.* (2016). ERRα regulated lactate metabolism contributes to resistance to targeted therapies in breast cancer, *Cell Reports* **15**(2), 323-335.

15. Cribb, J.; Osborne, L.D.; Beicker, K.; Psioda, M.; Chen, J.; O'Brien, E.T.; Taylor II, R.M.; Vicci, L.; Hsiao, J.P.L.; Shao, C.; Falvo, M.; Ibrahim, J.G.; **Wood, K.C.**; Blobe, G.C.; Superfine, R.* (2016). An Automated High-throughput Array Microscope for Cancer Cell Mechanics, *Sci. Rep.* **6**, 27371.

16. Lin, K.H.; Winter, P.S.; Xie, A.; Roth, C.; Martz, C.A.; Stein, E.M.; Anderson, G.R.; Tingley, J.P.; **Wood, K.C.*** (2016) Targeting MCL-1/BCL-X_L forestalls the acquisition of resistance to ABT-199 in acute myeloid leukemia *Sci. Rep*. **6**, 27696.

17. Anderson, G.R.; Wardell, S.E.; Cakir, M.; Crawford, L.; Leeds, J.C.; Nussbaum, D.N.; Shankar, P.S.; Soderquist, R.S.; Stein, E.M.; Tingley, J.P.; Winter, P.S.; Zeiser-Misenheimer, E.K.; Alley, H.M.; Yllanes, A.; Haney, V.; Blackwell, K.L.; McCall, S.J.; McDonnell, D.P.; **Wood, K.C.*** (2016). *PIK3CA* mutations enable targeting of a breast tumor dependency through mTOR-mediated MCL-1 translation, *Science Translational Medicine* **8**, 369ra175.

18. Price, A.M.; Dai, J.; Bazot, Q.; Patel, L.; Nikitin, P.A.; Djavadian, R.; Winter, P.S.; Salinas, C.A.; Perkins Barry, A.; **Wood, K.C.**; Johannsen, E.C.; Letai, A.; Allday, M.J.; Luftig, M.A.* (2017). Epstein-Barr virus ensures B cell survival by uniquely modulating apoptosis at early and late times after infection, *eLife* **6**, e22509.

19. Ali, M.[¶]; Kaltenbrun, E.[¶]; Anderson, G.R.[¥]; Stephens, S.J.[¥]; Arena, S.; Bardelli, A.; Counter, C.M.*; **Wood, K.C.*** (2017). Codon bias imposes a targetable limitation on *KRAS*-driven therapeutic resistance, *Nature Communications* **8**, 15617. ([¶]Co-first authors, [¥]Co-second authors)

20. Anderson, G.R.[¶]; Winter, P.S.[¶]; Lin, K.H.; Nussbaum, D.P.; Cakir, M.; Stein, E.M.; Soderquist, R.; Crawford, L.; Leeds, J.C.; Newcomb, R.; Stepp, P.; Yip, C.; Wardell, S.E.; Tingley, J.P.; Ali, M.; Xu, M.; Ryan, M.; McCall, S.J.; McRee, A.; Counter, C.M.; Der, C.J.; **Wood, K.C.*** (2017). A landscape of therapeutic cooperativity in *KRAS* mutant cancers reveals principles for controlling tumor evolution, *Cell Reports* **20**, 999-1015. ([¶]Co-first authors)

21. Singleton, K.R.[¶]; Crawford, L.[¶]; Tsui, E.; Manchester, H.E.; Maertens, O.; Liu, X.; Liberti, M.V.; Magpusao, A.N.; Stein, E.M.; Tingley, J.P.; Frederick, D.T.; Boland, G.M.; Flaherty, K.T.; McCall, S.J.; Krepler, C.; Sproesser, K.; Herlyn, M.; Adams, D.J.; Locasale, J.W.; Cichowski, K.; Mukherjee, S.; **Wood, K.C.**[*] (2017). Melanoma therapeutic strategies that select against resistance by exploiting MYC-driven evolutionary convergence, *Cell Reports* **21**, 2796-2812 ([¶]Co-first authors).

22. Crawford, L.A.*; **Wood, K.C.**; Zhou, X.; Mukherjee, S.* (2018). Bayesian approximate kernel regression with variable selection, *J. Am. Stat. Assoc.* **113**, 1710-1721.

23. Anderson, G.R.; Wardell, S.E.; Cakir, M.; Yip, C.; Ahn, Y.; Ali, M.; Yllanes, A.P.; Chao, C.A.; McDonnell, D.P.; **Wood, K.C.*** (2018). Dysregulation of mitochondrial dynamics proteins are a targetable feature of human tumors, *Nature Communications* **9**, 1677.

24. Ohiri, K.A.; Kelly, S.T.; Motschman, J.D.; Lin, K.H.; **Wood, K.C.**; Yellen, B.B.* (2018). A high throughput bulk acoustic wave device for the capture and compartmentalization of single cells, *Lab on a Chip* **18**, 2124-2133.

25. Soderquist, R.S.; Crawford, L.; Liu, E.; Lu, M.; Agarwal, A.; Anderson, G.R.; Lin, K.H.; Winter, P.S.; Cakir, M.; **Wood, K.C.*** (2018). Systematic mapping of BCL-2 gene dependencies in cancer reveals molecular determinants of BH3 mimetic sensitivity, *Nature Communications* **9**, 3513.

26. Ding, Y.; Gong, C.; Huang, D.; Chen, R.;; Sui, P.; Lin, K.H.; Liang, G.; Yuan, L.; Xiang, H.; Chen, J.; Yin, T.; Alexander, P.B.; Wang, Q.F.; Song, E.W.; Li, Q.-J.; **Wood, K.C.***; Wang, X.F.* (2018). Synthetic lethality between HER2 and transaldolase in intrinsically resistant HER2-positive breast cancers, *Nature Communications* **9**, 4274.

27. Lin, K.H.[¶]; Xie, A.[¶]; Rutter, J.C.; Ahn, Y.; Lloyd-Cowden, J.M.; Nichols, A.G.; Soderquist, R.S.; Koves, T.R.; Muoio, D.; MacIver, N.J.; Lamba, J.; Pardee, T.S.; McCall, C.M.; Rizzieri, D.A.; **Wood, K.C.*** (2019). Systematic dissection of the metabolic-apoptotic interface in AML reveals heme biosynthesis to be a regulator of therapeutic sensitivity, *Cell Metabolism* **29**, 1217-1231. ([¶]Co-first authors; May 2019 journal cover article)

28. Armstrong, A.J.*; Gupta, S.; Healy, P.; Kemeny, G.; Leith, L.; Zalutsky, M.R.; Spritzer, C.; Davies, C.; Rothwell, C.J.; Ware, K.E.; Somarelli, J.; **Wood, K.**; Riber, T.; Giannakakou, P.; Zhang, J.; Gerber, D.; Anand, M.; Foo, W.-C.; Halabi, S.; Gregory, S.G.; George, D.J. (2019) Pharmacodynamic study of radium-223 in men with bone metastatic castration resistant prostate cancer, *PLoS ONE* **14**, e0216934.

29. Cakir, M.; Mukherjee, S.*; **Wood, K.C.*** (2019). Label propagation defines signaling networks associated with recurrently mutated cancer genes, *Sci. Rep.* **9**, 9401.

30. Zhong, Z.; Sepramaniam, S.; Chew, X.H.; **Wood, K.**; Lee, M.A.; Madan, B.; Virshup, D.M.* (2019). PORCN inhibition synergizes with PI3K/mTOR inhibition in Wnt-addicted cancers, *Oncogene* **38**, 6662.

31. Manzari, M.T.; Anderson, G.R.; Lin, K.H.; Soderquist, R.S.; Cakir, M.; Zhang, M.; Moore, C.E.; Skelton, R.N.; Fevre, M.; Li, X.; Bellucci, J.J.; Wardell, S.E.; Costa, S.A.; **Wood, K.C.***; Chilkoti, A.* (2019). Genomically informed small molecule drugs overcome resistance to a sustained release formulation of an engineered death receptor agonist in patient-derived tumor models, *Science Advances* **5**, eaaw9162. (*Co-corresponding authors)

32. Liberti, M.V.; Allen, A.; Singleton, K.R.; Guo, Z.; Liu, J.O.; **Wood, K.C.**; Locasale, J.W.* (2019). Evolved resistance to partial GAPDH inhibition results in loss of the Warburg Effect and in a different state of glycolysis, *J Biol Chem* **295**, 111-124.

33. Lin, K.H.[¶]; Rutter, J.C.[¶]; Xie, A.; Pardieu, B.; Winn. E.T.; Dal Bello, R.; Forget, A.; Itzykson, R.; Ahn, Y.-R.; Dai, Z.; Sobhan, R.T.; Anderson, G.R.; Singleton, K.R.; Decker, A.E.; Winter, P.S.; Locasale, J.W.; Crawford, L.; Puissant, A.*; **Wood, K.C.*** (2020). Using antagonistic pleiotropy to design a chemotherapy-induced evolutionary trap to target drug resistance in cancer, *Nature Genetics* **52**, 408-417. ([¶]co-first authors, *co-corresponding authors). (Commentary: Lin, C.Y.* (2020). Springing an evolutionary trap on cancer, *Nature Genetics* **52**, 361-362.)

34. Ozkan-Dagliyan, I.; Diehl, J.N.; George, S.D.; Schaefer, A.; Papke, B.; Klotz-Noack, K.; Waters, A.M.; Goodwin, C.M.; Gautam, P.; Pierobon, M.; Peng, S.; Gilbert, T.S.K.; Lin, K.H.; Dagliyan, O.; Wennerberg, K.; Petricoin, E.F.; Tran, N.L.; Bhagwat, S.V.; Tiu, R.V.; Peng, S.B.; Herring, L.E.; Graves, L.M.; Sers, C.; **Wood, K.C.**; Cox, A.D.; Der, C.J.* (2020). Low-dose vertical inhibition of the RAF-MEK-ERK cascade causes apoptotic death of *KRAS* mutant cancers, *Cell Reports* 31, 107764.

35. Su, A.¶; Ling, F.¶; Vaganay, C.; Sodaro, G.; Benaksas, C.; Del Bello, R.; Forget, A.; Benajiba, L.; Pardieu, B.; Lin, K.H.; Rutter, J.C.; Bassil, C.F.; Fortin, G.; Pasanisi, J.; Antony-Debre, I.; Alexe, G.; Benoist, J.-F.; Pruvost, A.; Pikman, Y.; Qi, J.; Schlageter, M.H.; Micol, J.B.; Roti, G.; Cluzeau, T.; Dombret, H.; Preudhomme, C.; Fenouille, N.; Golan, H.M.; Stegmaier, K.; Lobry, C.*; **Wood, K.C.***; Itzykson, R.*; Puissant, A.* (2020). The folate cycle enzyme MTHFR is a critical regulator of cell response to MYC-targeting therapies, *Cancer Discovery* **10**, 1894-1911. (¶Co-first authors; *Co-senior authors).

(Commentary: Marando, L.; Huntly, B.J.P.* (2020). BETs need greens: Folate deficiency and resistance to MYC-targeted therapies, *Cancer Discovery* **10**, 1791-1793.)

36. Yellen, B.B.*; Zawistowski, J.S.; Czech, E.A.; Sanford, C.I.; SoRelle, E.D.; Luftig, M.A.; Forbes, Z.G.; **Wood, K.C.***; Hammerbacher, J.* (2021) Massively parallel quantification of phenotypic heterogeneity in single cell drug responses, *Science Advances* (In press) (*Co-corresponding authors).

37. Joh, D.Y.¶; Heggestad, J.T.¶; Zhang, S.¶; Anderson, G.R.; Bhattacharyya, J.; Wardell, S.E.; Wall, S.A.; Cheng, A.B.; Albarghouthi, F.; Liu, J.; Oshima, S.; Hucknall, A.M.; Hyslop; Hall, A.H.S.; **Wood, K.C.**; Hwang, E.S.; Strickland, K.C.; Wei, Q.*; Chilkoti, A.* (2021) Cellphone enabled point-of-care assessment of breast tumor cytology and molecular HER2 expression from fine-needle aspirates, *npj Breast Cancer* (In press) (¶Co-first authors; *Co-senior authors).

38. Lin, K.H.; Rutter, J.C.; Xie, A.; Vaganay, C.; Benaksas, C.; Meslin, P.A.; Benajiba, L.; Forget, A.; Itzykson, R.; Pierobon, M.; Lin, J.; Sheng, Z.; Li, X.; Chilkoti, A.; Owzar, K.; Rizzieri, D.A.; Pardee, T.S.; Petricoin, E.; Puissant, A.*; **Wood, K.C.*** (2021). P2RY2/AKT activation is a critical actionable consequence of nuclear export inhibition in acute myeloid leukemia, *Nature Cancer* (In minor revision).

39. Ali, M.; Lu, M.; Soderquist, R.S.; Glass, C.; Lopez, O.M.; Kerr, D.; Falcon, C.J.; Yu, H.A.; Hata, A.N.; Blakely, C.M.; McCoach, C.E.; Bivona, T.G.; **Wood, K.C.*** (2021). Targeted therapies induce an actionable caspase- and CAD-driven ATM dependence in residual tumors, *Science Translational Medicine* (In minor revision).

Reviews and commentaries

1. **Wood, K.C.**; Sabatini, D.M.* (2009). Growth signaling at the nexus of stem cell life and death, *Cell Stem Cell* **5**, 232-234.

2. **Wood, K.C.*** (2015). Mapping the pathways of resistance to targeted therapies, *Cancer Res.* **75**,4247-51.

3. **Wood, K.C.*** (2016). Intercepting reversible drug tolerance to improve targeted therapy, *Science Translational Medicine* **8**, 332ec52.

4. **Wood, K.C.*** (2016). Collaborating tumor cells overcome multitargeted antiangiogenic therapies, *Science Translational Medicine* **8**, 338ec77.

5. **Wood, K.C.*** (2016). Targeting the cancer cells that just won't go away, *Science Translational Medicine* **8**, 344ec101.

6. **Wood, K.C.*** (2016). Mapping a path for precision cancer therapies, *Science Translational Medicine* **8**, 348ec115.

7. **Wood, K.C.*** (2016). Two faces of circulating breast cancer cells, *Science Translational Medicine* **8**, 356ec149.

8. Singleton, K.R.; **Wood, K.C.*** (2016). Narrowing the focus: A toolkit to systematically connect oncogenic signaling pathways with cancer phenotypes, *Genes Cancer* **7**(7-8), 218-228.

9. **Wood, K.C.*** (2016). Hacking T cells with synthetic circuits to program antitumor responses, *Science Translational Medicine* **8**, 362ec172.

10. **Wood, K.C.*** (2016). An EXITS strategy for decreasing cancer risk in women, *Science Translational Medicine* **8**, 368ec197.

11. **Wood, K.C.*** (2017). Suppressing oncogenic transcription with a little healthy competition, *Science Translational Medicine* **9**, 374aaI5000.

12. Winter, P.S.; **Wood, K.C.*** (2018). Mapping effector-phenotype landscapes in KRAS-driven cancers, *Trends in Cancer* **4**, 333-335.

13. **Wood, K.C.*** (2020). Overcoming MCL-1-driven adaptive resistance to targeted therapies, *Nature Communications* **11**, 531.

Last updated: 9/3/2021

EXTERNAL INVITED TALKS

As a graduate student or postdoctoral fellow:

1. University of Texas-M.D. Anderson Cancer Center, Dept. of Genitourinary Medical Oncology, 2006.
2. University of California-Berkeley, Dept. of Chemical Engineering, 2007 (Dept. Seminar).
3. Georgia Institute of Technology, Dept. of Chemical Engineering, 2007 (Dept. Seminar).
4. MIT, Dept. of Chemistry, 2008 (Small Talks Seminar Series).
5. MIT, Dept. of Electrical Engineering and Computer Science, 2008 (MEMS@MIT Spring Symposium).
6. Broad Institute of Harvard and MIT, 2009 (Annual Meeting of the Board of Scientific Counselors).
7. Broad Institute of Harvard and MIT, 2009 (Annual Scientific Retreat).
8. Ohio State University, Dept. of Chemical and Biomolecular Engineering, 2012 (Dept. Seminar).
9. University of Virginia, Dept. of Biomedical Engineering, 2012 (Dept. Seminar).
10. University of Pennsylvania, Dept. of Bioengineering, 2012 (Dept. Seminar).
11. Washington University School of Medicine, Dept. of Genetics, 2012 (Dept. Seminar).
12. Harvard Medical School, Massachusetts General Hospital, Dept. of Pathology, 2012 (Dept. Seminar).
13. Duke University, Dept. of Pharmacology and Cancer Biology, 2012 (Dept. Seminar).

As a faculty member:

14. Institute for Biological Engineering Annual Meeting, Raleigh, NC, 2013.
15. Forbeck Scholars Retreat, Hilton Head, SC, 2013.
16. University of North Carolina-Chapel Hill, Dept. of Pharmacology, Chapel Hill, NC, 2014.
17. University of Texas Medical Branch-Galveston, Dept. of Pharmacology, Galveston, TX, 2014.
18. National Cancer Institute-Frederick, Ras Program, Frederick, MD, 2014.
19. Dana-Farber Cancer Institute, Bone Marrow Transplant Grand Rounds, Boston, MA, 2014.
20. Whitehead Institute for Biomedical Research, Fall Whitehead Forum Seminar Series, Cambridge, MA, 2014.
21. UNC-Chapel Hill, Lineberger Comprehensive Cancer Center Fall Seminar Series, Chapel Hill, NC, 2014.
22. American Association for Cancer Research (AACR) Annual Meeting, Phenotypic Screening for Optimizing Cancer Therapy, Philadelphia, PA, 2015.
23. UNC/HHMI Translational Medicine Symposium, Keynote address, Chapel Hill, NC, 2015.
24. Mount Sinai School of Medicine, Dept. of Oncological Sciences, New York, NY, 2015.
25. *The Scientist* Webinar: Tools and Strategies to Study Cell Signaling Pathways, 2015 (virtual).
26. Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH, 2016.
27. 40th Annual UNC Lineberger Cancer Center Symposium, "Molecularly targeted therapies from bench to bedside", Chapel Hill, NC, 2016.
28. American Association for Cancer Research (AACR) Annual Meeting, State of the Art Approaches to Study Resistance to Targeted Therapies, New Orleans, LA, 2016.
29. University of Pennsylvania, Abramson Family Cancer Research Institute and the Department of Hematology/Oncology, Philadelphia, PA, 2016.
30. American Association for Cancer Research (AACR) Precision Medicine Series: Opportunities and Challenges of Exploiting Synthetic Lethality in Cancer, San Diego, CA, 2017.
31. New York University, Laura and Isaac Perlmutter Cancer Center, Research Seminar Series, New York, NY, 2017.
32. ASBMB Annual Meeting, Cancer Signaling and Therapeutics section, Chicago, IL, 2017.
33. 32nd Aspen Cancer Conference, Aspen, CO, 2017.
34. Pfizer Oncology, La Jolla, CA, 2017.
35. Center for Cell Reprogramming at Georgetown University Medical Center, Research Seminar Series, Washington, DC, 2018.
36. National Institute of Environmental Health Sciences (NIEHS), Receptor Mechanisms Discussion Group (RMDG), Research Triangle Park, NC, 2018.
37. Ludwig Institute, Harvard Medical School, Boston, MA, 2018.

38. UCSF Helen Diller Family Comprehensive Cancer Center Friday Seminar, San Francisco, CA, 2018.
39. University of California, San Diego, Cancer Center Genomics Program Research Seminar, La Jolla, CA, 2018.
40. Broad Institute of Harvard and MIT, Innovators in Cancer Seminar Series, Cambridge, MA, 2018.
41. Moffitt Cancer Center, Basic Science Grand Rounds, Tampa, FL, 2019.
42. Venetian Institute of Molecular Medicine, University of Padova, Italy, 2019.
43. NCI Physical Sciences-Oncology Network (PS-ON) and Cancer Systems Biology Consortium (CSBC) Annual Junior Investigators' Meeting (Keynote lecturer), Shady Grove, MD, 2019.
44. Cold Spring Harbor Laboratory Meeting: Cell Death, Cold Spring Harbor, NY, 2019.
45. Quantitative Biology of the Cancer Cell Symposium, UCSF/UCSD Cancer Cell Mapping Initiative, San Francisco, CA, 2020.
46. Sixth AACR-IASLC International Joint Conference: Lung Cancer Translational Science from the Bench to the Clinic, San Diego, CA, 2020.
47. LabRoots 8th Annual Genetics Virtual Week, Precision Medicine Symposium, 2020 (virtual).
48. St. Jude Children's Research Hospital, Dept. of Cell and Molecular Biology, Memphis, TN, 2020 (virtual).
49. Dana-Farber / Harvard Cancer Center (DFHCC) Connect:Science Seminar Series, Boston, MA, 2020 (virtual).
50. Virtually Dead Episode I: Mitochondria Symposium, 2020 (virtual).
51. Peter MacCallum Cancer Centre Seminar Series, Melbourne, Australia, 2021 (virtual).
52. Syros Pharmaceuticals, Cambridge, MA, 2021 (virtual).
53. V Scholar Summit, Speaker and panelist, SAS Institute, Raleigh, NC, 2021 (virtual).
54. AACR Annual Meeting, Session on Therapy Resistance in Leukemia, 2021 (virtual).
55. Vanderbilt University, Dept. of Pathology, Microbiology, and Immunology, Nashville, TN, 2021 (virtual).