

AWARD NUMBER: W81XWH-21-1-0522

TITLE: Targeting Histone Lysine Demethylase KDM4A in Neuroendocrine Prostate Cancer

PRINCIPAL INVESTIGATOR: Dr. Guocan Wang, PhD

CONTRACTING ORGANIZATION: The University of Texas MD Anderson Cancer Center

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14. ABSTRACT Neuroendocrine prostate cancer represents a highly lethal subtype of castration resistant prostate cancer (CRPC) that lacks effective treatment options. Despite the low incidence of de novo NEPC, the incidence of treatment-related NEPC (t-NEPC) is on the rise, which emerges in prostate adenocarcinoma treated with potent androgen receptor pathway inhibitors as a mechanism of therapeutic resistance. We identified histone lysine demethylase KDM4A as a epigenetic regulator that is highly expressed in NEPC. Our research focuses on the role of 4A in tumor progression of neuroendocrine prostate cancer (NEPC), the mechanisms by which KDM4A drives NEPC progression, and the efficacy of KDM4 inhibitor as monotherapy and combination therapy in NEPC.					
15. SUBJECT TERMS Prostate cancer, castrate-resistant prostate cancer, epigenetics, histone lysine demethylase, neuroendocrine prostate cancer					
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September 1, 2022 to August 31, 2023

1. INTRODUCTION

Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Neuroendocrine prostate cancer (NEPC) represents a highly lethal subtype of castration-resistant prostate cancer (CRPC) that lacks effective treatment options. Despite the low incidence of de novo NEPC, treatment-related NEPC (t-NEPC) has been increasingly observed in patients with prostate adenocarcinoma as a mechanism of therapeutic resistance, who receive potent androgen receptor pathway inhibitor treatment. We identified histone lysine demethylase KDM4A as a critical epigenetic regulator that is highly expressed in NEPC. Our research focuses on the role of KDM4A in the tumor progression of NEPC, the mechanisms by which KDM4A drives NEPC progression, and the efficacy of KDM4 inhibitor(s) as monotherapy and combination therapy in NEPC.

2. KEYWORDS

Provide a brief list of keywords (limit to 20 words).

Prostate cancer, castrate-resistant prostate cancer, epigenetics, histone lysine demethylase, neuroendocrine prostate cancer

3. ACCOMPLISHMENTS

The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Specific Aim 1: Determine the role of KDM4A in NEPC progression using organoids, PDXs, and GEMMs	Proposed Timeline (Months)	Status (Completion dates or percentage of completion)
Major Task 1: Determine the role of KDM4A using organoid		
Subtask 1: Local institutional animal care and use committee (IACUC) and USAMRDC Animal Care and Use Review Office (ACURO) approval We will amend our IACUC protocol #00001713-RN01	1-3	100% complete Received ACURO's approval on 05/07/2021
Subtask 2: local institutional review board (IRB) and USAMRDC Human Research Protection Office (HRPO) We will amend our existing protocol # PA12-0594 and LAB09-0018 as needed	1-3	100% complete Received HRPO approval on 08/12/2021
Subtask 3: Implant and passage PDXs in SCID mice MDA PCa 144-13 and MDA PCa 155- PDXs will be obtained from Dr. Nora Navone and implanted into SCID mice.	4-9	100% complete
Subtask 4: Analysis of the effect of KDM4A knockdown and KDM4 inhibitors on MSK-PCa4 organoid line We will determine the function of KDM4A in an organoid line.	4-13	100% complete
Subtask 5: Generate and expand organoids from PDXs MDA PCa 144-13 and MDA PCa 155- PDXs will be harvested to generate organoids; Organoids will be expanded	7-13	100% complete

Subtask 6: Test the effect of KDMA KD and KDM4 inhibitors on the growth and apoptosis of organoids KDM4A shRNA and KDM4 inhibitors will be used to test the function of KDM4A in proliferation and apoptosis	14-24	100% complete
<i>Milestone(s) Achieved: establishing a key functional role for KDM4A in NEPC progression in organoid models</i>	24	
Major Task 2: Determine the role of KDM4A using the conditional knockout (cKO) mouse model		
Subtask 1: Generate Pb-Cre4;KDM4A fl/fl;TRAMP (KT) mice and TRAMP mice for survival analysis & histological progression analysis KT and TRAMP will be generated through breeding in Wang lab (40 mice/genotype)	4-18	100% complete
Subtask 2: Histopathological analysis of KT & TRAMP mice Tumor will be subjected to histopathological analysis	4-25	60% complete. It will be continued in the next year.
<i>Milestone(s) Achieved: establishing a key functional role for KDM4A in NEPC progression in cKO model</i>	25	
Specific Aim 2: Determine the mechanism(s) by which KDM4A regulate UPR signaling		
Major Task 3: Determine the whether KDM4A directly regulates ATF3, DDIT3, c-JUN transcription		
Subtask 1: Validate KDM4A antibodies for ChIP analysis Test KDM4A antibodies for ChIP-seq in pilot experiments; Cell lines: 144-13 generated at MD Anderson; PSTR, PTR cells generated in Wang lab from NEPC GEMMs	1-3	100% complete
Subtask 2: Perform ChIP-qPCR of KDM4A and histone modifications in NEPC cells Perform ChIP-qPCR in NEPC cell lines	4-8	0% complete because this experiment is not needed based on ChIP-seq data.
Subtask 3: Perform ChIP-seq analysis of KDM4A and Histone modification in NEPC cells. ChIP-seq to identify KDM4A target genes	9-14	100% complete
Subtask 4: Analyzed publicly available and in-house microarray, RNA-seq, ChIP-seq of human and NEPC Bioinformatic analysis to identify molecular mechanism	9-13	100% complete
<i>Milestone(s) Achieved: establishing ATF3, DDIT3,c-JUN as KDM4A target genes & identifying other KDM4A target genes</i>	13	100% complete
Major Task 4: Determine the role of KDM4A in the regulation of the ER stress and UPR		
Subtask 1: measure ER dilation using electron microscopy To examine effect of KDM4 inhibitor on ER stress	1-13	100% complete
Subtask 2: Examine ER stress response in cell lines <i>in vitro</i> ER stress response and UPR signaling will be analyzed by western blot and qPCR in NEPC and ARPC cell lines	1-13	100% complete

<i>Milestone(s) Achieved: establishing a role for KDM4A in ER stress and UPR signaling</i>	13	
Major Task 5: Determine the correlation of KDM4A expression with UPR signaling in NEPC and ARPC		
Subtask 1: Validate antibodies for proteins in UPR signaling Various antibodies will be validated in IHC staining	9-12	100% complete
Subtask 2: Acquire human prostate tumor samples. <i>Source of biospecimens:</i> Dept. of Genitourinary Medical Oncology or the PCBN cohort. Identifiable information is only accessible to the Drs. Aparicio, Troncoso, & Zhang (Pilot study: 10 cases each low-grade hormone-naïve, high-grade hormone-naïve, adeno-CRPC, NEPC; primary tumor)	13-18	100% complete
Subtask 3: IHC staining of human prostate tumor tissues for ER stress markers and KDM4A Tumors from above will be stained by IHC	19-28	30%. It will be continued in the next year.
Subtask 5: Analyze IHC staining results IHC staining data from above will be analyzed	29-36	
<i>Milestone(s) Achieved: characterization of KDM4A expression and UPR signaling in human tumor samples</i>	36	
Specific Aim 3: Determine whether KDM4 inhibitors improve the therapeutic outcomes of platinum-taxane chemotherapy in NEPC		
Major Task 6: Examine whether QC6352 enhance the response of NEPC to cabazitaxel (CBTX) and carboplatin (CARB) in GEMM		
Subtask 1: Examine dose response of CARB using PSTR cells SubQ implanted mice will be treated with different doses of CARB (20 male nude mice, Jackson Lab)	7-12	100% complete
Subtask 2: Examine whether QC6352 enhance the response of NEPC to CBTX and CARB in GEMM NEPC GEMMs will be treated with QC6352, CARB, CBTX (120 male NEPC GEMMs generated in Wang lab)	11-28	50% complete. It will be continued in the next year.
Subtask 3: Histopathological analysis of treated GEMM tumor H & E & IHC staining of treated tumors.	29-36	
<i>Milestone(s) Achieved: establishing the efficacy of KDM4 inhibitor combination therapy in GEMMs</i>	36	
Major Task 7: Examine whether QC6352 enhance the response of NEPC to CBTX and CARB in PDXs		
Subtask1: Examine whether QC6352 enhance the response of NEPC to CBTX and CARB in PDX SCID mice with NEPC PDXs in will be treated with QC6352, CARB, CBTX (240 male SCID mice, Jackson Lab)	11-28	50% complete. It will be continued in the next year.
Subtask 2: Histopathological analysis of treated PDX H & E & IHC staining of treated tumors	29-36	
<i>Milestone(s) Achieved: establishing the efficacy of KDM4 inhibitor combination therapy in PDXs</i>	36	

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

1. Major activities

- Performing functional and mechanistic studies to delineate the function of KDM4A *in vitro* and *in vivo* using cell lines, organoids, PDXs, and GEMMs.
- Continuing the analysis of ChIP-seq, microarray, and RNA-Seq data generated from human and mouse prostate cancer to elucidate the mechanisms by which KDM4A drives NEPC progression and regulates unfolded protein response.
- Demonstrating the efficacy of KDM4 inhibitor QC6352 as monotherapy and combination therapy.

2. Specific objectives

Aim 1. Determine the role of KDM4A in NEPC progression using organoids, PDXs, and GEMMs.

Aim 2. Examine the mechanism(s) by which KDM4A regulates UPR signaling.

Aim 3. Determine whether KDM4 inhibitors improve the therapeutic outcomes of platinum-taxane chemotherapy in NEPC.

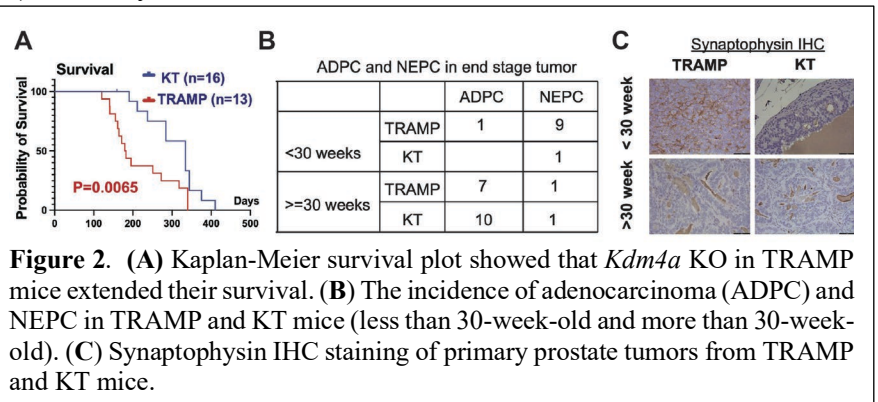
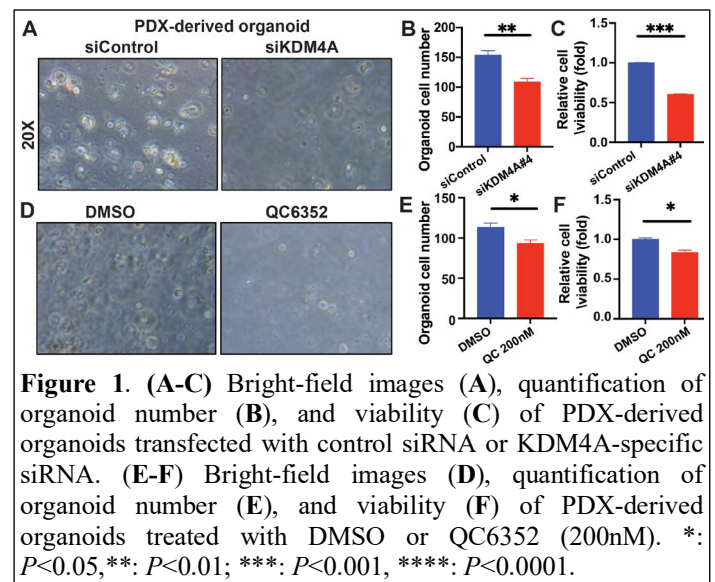
3. Significant results/key outcomes

Aim 1. Determine the role of KDM4A in NEPC progression using organoids, PDXs, and GEMMs.

(a) *KDM4A* knockdown (KD) or inhibition suppressed the growth NEPC PDX-derived organoids *in vitro*. To determine whether KDM4A plays an important role in the growth of NEPC organoids *in vitro*, transfected a validated KDM4A-specific siRNA with high KD efficiency into PDX-derived organoids (MDA PCa 155-2 and MDA PCa 144-13). We found that *KDM4A* KD led to a dramatic reduction in the number of organoids and cell viability as measured by CellTiter-Glo® 3D Cell Viability Assay (Promega) (**Figure 1A-C & data not shown**). Treatment of PDX-derived organoids with KDM4 inhibitor (KDM4i) QC6352 (200 nM) similarly led to a significant reduction in the number of organoids and cell viability (**Figure 1D-F**).

(b) *Kdm4a* KO prolonged overall survival in KT mice and reduced NEPC incidence. We have generated 16 Pb-Cre4;*KDM4A*^{fl/fl};TRAMP (KT) mice and 13 TRAMP mice for survival analysis and histological progression analysis. Any mice that reached the study endpoint have been euthanized and subjected to

histopathological analyses using H & E and IHC staining. *Kdm4a* KO led to a significant increase in the median survival of KT mice compared to TRAMP mice (**Figure 2A**). Also, we examined the prostate tumors from KT mice and TRAMP mice collected from the survival cohort for the presence of NEPC using H & E staining and



synaptophysin IHC. We found that the incidence of NEPC is dramatically reduced in KT mice compared to TRAMP mice (**Figure 2B-C**). For mice that died before 30 weeks, the majority of the TRAMP mice had NEPC whereas KT mice rarely died before 30-week-old. Interestingly, for mice that died after 30 weeks, both TRAMP and KT mice mainly developed adenocarcinoma (**Figure 2B-C**).

Aim 2. Examine the mechanism(s) by which KDM4A regulates UPR signaling.

(a) RNA-seq analysis of KDM4A-KD 144-13 cells and control 144-13 cells to identify the genes and pathways regulated by KDM4A in human NEPC cells. We previously performed RNA-seq analysis of mouse PTR cells infected with *Kdm4a*-specific lentiviral shRNA and control shRNA. To determine whether the genes and pathways regulated by KDM4A in mouse NEPC cells are also conserved in human NEPC cells, we knocked down KDM4A in 144-13 cells using siRNA (**Figure 3A**), followed by RNA-seq analysis of KDM4A-KD 144-13 cells and control 144-13 cells with 3 replicates (GSE GSE241431). Heatmap showed that the 3 replicates have similar gene expression profiles (**Figure 3B**). We identified a total of 1333 upregulated genes and a total of 1767 downregulated genes in *KDM4A*-KD 144-13 cells compared to control 144-13 cells (cut off: $P \leq 0.05$, fold change ≥ 1.5) (**Figure 3C**). In our previous progress report, we showed that JUN and ATF3 but not DDIT3 are KDM4A direct target genes in 144-13 cells as shown by KDM4A ChIP-seq analysis. Consistent with this observation, JUN and ATF3 mRNAs were upregulated in *KDM4A*-KD cells (**Figure 3D**). Also, Gene Set

Enrichment Analysis (GSEA) using a list of genes involved in unfolded protein response (UPR) (QuickGO database) showed that UPR pathway is activated in *KDM4A*-KD 144-13 cells (**Figure 3E**). This finding is consistent with our RNA-seq data on mouse PSTR cells treated with KDM4 inhibitor QC6352 (see the preliminary data in the funded proposal).

(b) MYC, interferon alpha signaling, and interferon gamma signaling were deregulated in KDM4A-KD 144-13 cells. Since we previously identified common pathways regulated KDM4A in mouse PTR cells and TNBC cells through RNA-seq analysis of a publicly available RNA-seq dataset (GSE95293: KDM4i vs control in TNBC) and an in-house RNA-seq datasets (*Kdm4a*-KD PTR cells and control cells) (GSE227717, see our previous report). We found that MYC, interferon alpha signaling, and interferon gamma signaling were also deregulated in *KDM4A*-KD 144-13 cells, with MYC signaling downregulated and interferon alpha signaling and interferon gamma signaling upregulated (**Figure 4A**). Together, these data suggest that KDM4A regulates common pathways across human and mouse NEPC.

(c) MYC is activated in both human and mouse NEPC. Although ATF3 and JUN are well-

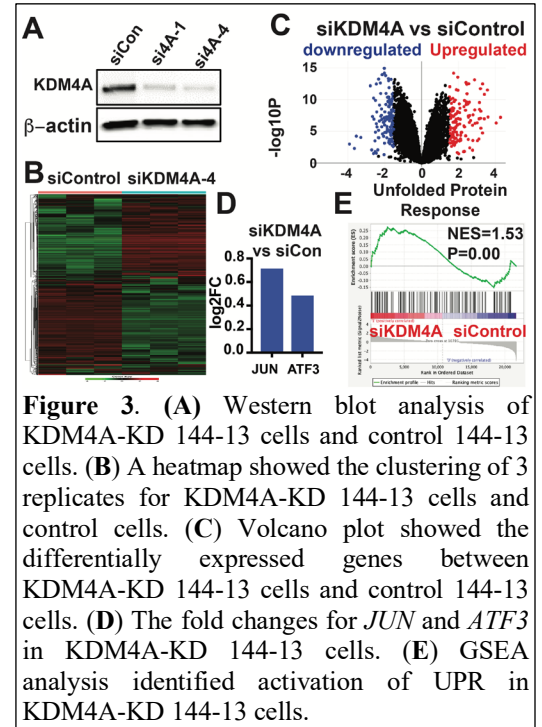


Figure 3. (A) Western blot analysis of KDM4A-KD 144-13 cells and control 144-13 cells. (B) A heatmap showed the clustering of 3 replicates for KDM4A-KD 144-13 cells and control cells. (C) Volcano plot showed the differentially expressed genes between KDM4A-KD 144-13 cells and control 144-13 cells. (D) The fold changes for *JUN* and *ATF3* in KDM4A-KD 144-13 cells. (E) GSEA analysis identified activation of UPR in KDM4A-KD 144-13 cells.

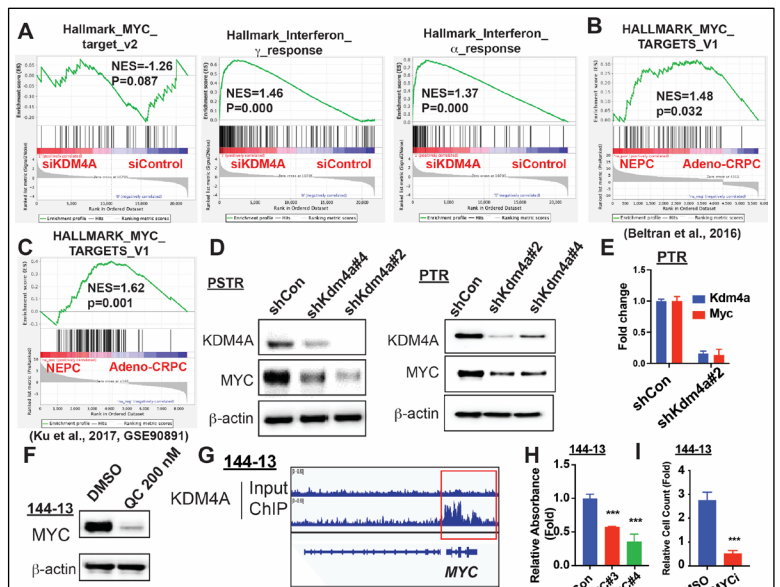


Figure 4. (A) GSEA analysis showed that MYC signaling was downregulated and interferon alpha and gamma signaling was activated in KDM4A-KD 144-13 cells. (B-C) GSEA showed that MYC signaling is activated in human (B) and mouse (C) NEPC compared to prostate adenocarcinoma. (D) Western blot showed that MYC expression is downregulated in *Kdm4a*-KD PSTR and PTR cells. (E) qRT-PCR showed that *Myc* mRNA expression is downregulated in *Kdm4a*-KD PTR cells. (F) Western blot analysis showed that KDM4A inhibition by QC6352 led to reduced MYC expression. (G) KDM4A ChIP-seq showed that *MYC* is a direct target of KDM4A. (H-I) *MYC* knockdown with siRNA (H) or inhibition using MYC inhibitor (MYCi975) (I) reduced the proliferation of 144-13 cells.

characterized UPR genes, we examined other additional genes and pathways that may also regulate UPR. Interestingly, MYC has been shown to be a powerful oncogene in many cancer types, including prostate cancer, and has been shown to play an important role in UPR. However, the role of MYC in NEPC is not well characterized, despite that it has been implicated in NEPC pathogenesis. Park et al. showed that a combination of perturbation of the expression of 5 genes, including MYC, transformed normal prostate epithelial into NEPC (*Science* 2018), suggesting a critical role of MYC in NEPC progression. We then performed GSEA analysis of Beltran et al. human PCa dataset (*Nat Med* 2016) and Ku et al. mouse PCa RNA-seq dataset (*Science* 2017) and found that MYC is activated in both human and mouse NEPC (**Figure 4B-C**). Thus, our findings suggest that MYC may be an important player in NEPC progression.

(d) *Validating c-MYC as a direct target gene which regulates proliferation and unfolded protein response in NEPC cells.* Since KDM4A regulates MYC signaling, we first determined whether the decrease in MYC signaling in KDM4A-KD cells is due to the reduction in MYC expression. We examined the effect of KDM4A KD or inhibition on MYC mRNA expression. We found that KDM4A KD in human 144-13 cells and mouse PTR cells led to a significant reduction in MYC protein expression and mRNA expression (**Figure 4D-E**). Also KDM4 inhibitor QC6352 treatment also reduced MYC expression (**Figure 4F**). Since KDM4A is a histone lysine demethylase that regulates transcription, we first analyzed our KDM4A ChIP-seq data to determine whether MYC is a direct target gene of KDM4A. Indeed, we found that KDM4A binds to MYC loci (**Figure 4G**). We further examined the effect of MYC KD and inhibition on NEPC proliferation. We found that both MYC KD with siRNA and inhibition using MYC inhibitor MYCi975 significantly reduced NEPC proliferation (**Figure 4H-I**).

(e) *Measuring ER dilation using Transmission Electron Microscopy (TEM).* We performed TEM analysis of *Kdm4a*-KD PTR cells, QC6352-treated PTR cells (200 nM, 500 nM), Tunicamycin-treated (1 μ M), and DMSO-treated PTR cells as control at MD Anderson High Resolution Electron Microscopy Facility (HREMF). Tunicamycin is a well-established ER stress inducer and was used as a positive control. Also, low serum was used to increase the cellular stress due to the reduced availability of nutrients. We found that both *Kdm4a* KD and QC6352 treatment led to dilated ER (**Figure 5**), supporting our hypothesis that KDM4A plays an important role in the regulation of ER stress and unfolded protein response. Also, low serum condition (1%) FBS seems to exacerbate the ER stress in *Kdm4a*-KD cells.

Aim 3. Determine whether KDM4 inhibitors improve the therapeutic outcomes of platinum-taxane chemotherapy in NEPC.

(a) *QC6352 improved the response of PSTR GEMM to cabazitaxel (CBTX).* We treated PSTR GEMM

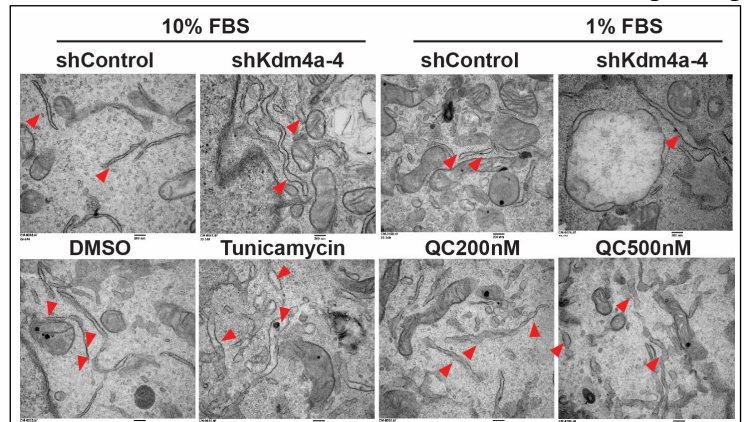


Figure 5. Transmission electron microscopy (TEM) images of *Kdm4a*-KD and control PTR cells cultured in either 10% FBS or 1% FBS, and PTR cells (cultured in 10% FBS) treated with DMSO, Tunicamycin, an ER stress inducer as a positive control, and QC6352. The red arrowheads indicate the ER. In the *Kdm4a*-KD cells, Tunicamycin-treated cells, and QC-treated cells, there is an enlargement of ER lumen, indicating the presence of ER stress.

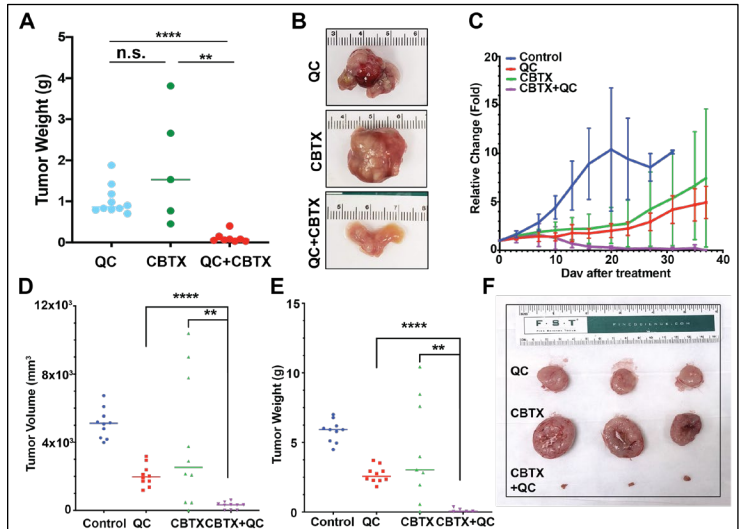


Figure 6. (A-B) Tumor weights and representative images of the prostate tumors from PSTR model after treatment with QC, cabazitaxel (CBTX), and QC + CBTX. (C) Tumor volumes of the 144-13 subQ tumors treated with vehicle control, QC, CBTX, and CBTX+QC. (D-E) Tumor volumes (D), tumor weights (E), and representative images (F) of tumors harvested from the treated mice at the end point of the experiments. Note: mice treated with vehicle control had big tumor burdens and were euthanized earlier than other groups.

with QC, cabazitaxel, and QC + cabazitaxel. We found that QC6352 treatment dramatically improved the response of PSTR GEMM to cabazitaxel, resulting in a significant reduction in tumor burden (**Figure 6A-B**).

(b) QC6352 improved the response of NEPC 144-13 cell line subcutaneous (subQ) tumors and MDA PCa 144-13 PDXs to cabazitaxel. We also tested the effect of QC6352 on the response of 144-13 cell line subQ tumors and MDA PCa 144-13 PDX to cabazitaxel. Male nude mice (Jackson Lab) bearing subQ implanted tumors were treated with QC6352 and cabazitaxel when the volume reaches 400 mm³. Tumor sizes were monitored by weekly measurement. We found that QC6352 combined with cabazitaxel led to a more profound reduction in the tumor volume and tumor weights compared to QC or cabazitaxel in 144-13 cell line subQ tumors and MDA PCa 144-13 PDXs (**Figure 6C-F & data not shown**).

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

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to Report.

How were the results disseminated to communities of interest?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to Report.

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

If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Aim 1. Perform histopathological analysis of prostate tumors from the KT and TRAMP mice.

Aim 2. Continue IHC staining of human prostate tumor tissues for ER stress markers and KDM4A tumors and analyze IHC staining results.

Aim 3. Determine whether KDM4 inhibitors improve the therapeutic outcomes of carboplatin chemotherapy in NEPC GEMM and PDX.

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:

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

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

The findings from this funded project are likely to lead to a clinical trial by Tachyon Therapeutics, which has a phase 1/1b clinical trial, in NEPC.

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report.

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including: transfer of results to entities in government or industry; instances where the research has led to the initiation of a start-up company; or adoption of new practices.

Nothing to Report.

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- improving public knowledge, attitudes, skills, and abilities;
- changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or
- improving social, economic, civic, or environmental conditions.

Nothing to Report.

5. CHANGES/PROBLEMS

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

Nothing to Report

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to Report.

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

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Nothing to Report.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated..

Nothing to Report.

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. PRODUCTS

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."

- **Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award.

Journal publications. List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume; year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).

Celia Sze Ling Mak, Ming Zhu, Xin Liang, Feng Wang, Anh G Hoang, Xinzhi Song, Peter Shepherd, Derek Liang, Jessica Suh, Jiwon Park, Miao Zhang, Eric Metzger, Roland Schüle, Abhinav K. Jain, Ellen Karasik, Barbara A. Foster, Min Gyu Lee, Paul Corn, Christopher J. Logothetis, Ana Aparicio, Nora Navone, Patricia Troncoso, Jianhua Zhang, Sue-Hwa Lin, **Guocan Wang**. KDM4A promotes the progression of neuroendocrine prostate cancer. *Oncogene* [under review, also deposited into bioRxiv, bioRxiv 2022.05.14.491739 (2023).

Conference Poster

Celia Sze Ling Mak, Ming Zhu, Xin Liang, Feng Wang, Anh G. Hoang, Xinzhi Song, Peter Shepherd, Derek Liang, Jessica Suh, Jiwon Park, Miao Zhang, Eric Metzger, Roland Schule, Abhinav K. Jain, Ellen Karasik, Barbara A. Foster, Min Gyu Lee, Paul Corn, Christopher J. Logothetis, Ana Aparicio, Nora Navone, Patricia Troncoso, Jianhua Zhang, Sue-Hwa Lin, Guocan Wang. KDM4A promotes NEPC progression through regulation of MYC expression. [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2023; Part 1 (Regular and Invited Abstracts); 2023 Apr 14-19; Orlando, FL. Philadelphia (PA): AACR; Cancer Res 2023;83(7_Suppl):Abstract nr 4760.

Books or other non-periodical, one-time publications. Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).

Nothing to Report.

Other publications, conference papers and presentations. Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.

Invited Speaker: "Histone Lysine Demethylase KDMA4 as a Driver in Neuroendocrine Prostate Cancer", Agilent BioTek Augmented Microscopy Virtual Summit, 4/27/2023

- **Website(s) or other Internet site(s)**

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to Report.

- **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

Nothing to Report.

- **Inventions, patent applications, and/or licenses**

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to Report.

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include: data or databases; biospecimen collections; audio or video products; software; models; educational aids or curricula; instruments or equipment; research material (e.g., Germplasm; cell lines, DNA probes, animal models); clinical interventions; new business creation; and other.

- **Data or databases:** (1) an RNA-seq data generated from *Kdm4a* KD PTR cells and control PTR cells (GSE227717); (2) a ChIP-seq dataset from 144-13 cells using antibodies for KDM4A, H3K9me3, H3K27ac, H3K36me3, and CTCF (GSE227688); (3) an RNA-seq data generated from *KDM4A* KD 144-13 cells and control 144-13 cells (GSE241431)
- **Research material:** (1) mouse NEPC cell lines PTR and PSTP; (2) *Kdm4a* prostate specific KO mouse model [Pb-Cre4;KDM4A^{fl/fl};TRAMP (KT)].

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

The following individuals worked on this grant during 09/01/2022-08/31/2023.

Name:	Guocan Wang
Project Role:	Principal Investigator
Research Identifier (e.g. ORCID ID):	0000-0002-8922-7249
Nearest Person Months Worked:	4 calendar months
Contribution to Project:	Dr. Wang is responsible for the overall oversight and direction of this proposal.
Funding Support: Complete only if the funding support is provided other than this award.	N/A

Name:	Ana Aparicio
Project Role:	Co-Investigator
Research Identifier (e.g. ORCID ID):	000-0003-0900-0923
Nearest Person Months Worked:	1 calendar month
Contribution to Project:	Dr. Aparicio coordinates the sample assembly and distribution, and oversees the data analysis and interpretation related to the tissue correlates on these studies.

Funding Support:	N/A
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Name:	Min Gyu Lee
Project Role:	Co-Investigator
Research Identifier (e.g. ORCID ID):	0000-0003-0859-0642
Nearest Person Months Worked:	1 calendar month
Contribution to Project:	Dr. Lee has vast experience in epigenetics including histone lysine demethylases. He assists Dr. Wang and his team in the epigenetic profiling experiments and assays for histone lysine demethylase activities.
Funding Support:	N/A

Name:	Ming Zhu
Project Role:	Postdoctoral Fellow (9/1/2022-6/30/2023) Research Scientist (7/1/2023-8/31/2023)
Research Identifier (e.g. ORCID ID):	N/A
Nearest Person Months Worked:	6 calendar months (9/1/2022-6/30/2023) 12 calendar months (7/1/2023-8/31/2023)
Contribution to Project:	Ming Zhu assists Dr. Wang to further perform in vivo animal experiments to determine the efficacy of KDM4A in NEPC progression using organoid, patient-derived xenograft (PDX), and genetically engineered mouse models (GEMMs). Also, Ming works with the collaborations to elucidate the mechanisms by which KDM4A promote NEPC progression. Lastly, she tests the efficacy of combination therapy in PDX and GEMM.
Funding Support:	N/A

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

If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) 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. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

WANG, Guocan

CURRENT

(NEW)

Bridge Funding

(Wang)

Title:

KDM4A in the Metastasis of Neuroendocrine Prostate Cancer

Effort:

0.60 calendar months (5%) - unsalaried

Supporting Agency:

MD Anderson

Grants Officer:

Carrie C. Feighl

Performance Period:

06/01/2023-05/31/2024

Level of Funding:

Project Goals:

Our objectives are to delineate the roles of KDM4A in NEPC metastasis and to evaluate the efficacy of KDM4 inhibitor-based mono- and combination therapy in delaying/reducing distant metastasis and treating established metastasis in preclinical models.

Specific Aims:

1) Determine the role of KDM4A in NEPC metastasis in vivo. 2) Determine the chromatin-dependent functions of KDM4A in promoting NEPC metastasis. 3)

Determine the chromatin-independent functions of KDM4A in promoting NEPC metastasis. 4) Determine the efficacy of KDM4 inhibitor-based therapies in delaying or preventing metastasis and treating established metastasis in NEPC preclinical models.

Role: Principal Investigator
Overlap: None

(THIS AWARD)

Grant No (PI): W81XWH-21-1-0522 (Wang)
Title: PC200420: Targeting Histone Lysine Demethylase KDM4A in Neuroendocrine Prostate Cancer

Effort: 3.60 calendar months (30%)

Supporting Agency: DOD-PCRP Idea

Grants Officer: Kimberly Carter

Performance Period: 09/01/2021-08/31/2024

Level of Funding:

Project Goals: Our overall goal is to develop combination therapy to improve the clinical outcome of platinum-taxane chemotherapy in patients with NEPC.

Specific Aims: 1) Determine the role of KDM4A in NEPC progression using organoids, PDXs, and GEMMs. 2) Examine the mechanism(s) by which KDM4A regulates UPR signaling. 3) Determine whether KDM4 inhibitors improve the therapeutic outcomes of platinum-taxane chemotherapy in NEPC.

Role: Principal Investigator

Overlap: None

(NEW)

HT9425-23-1-0305 (Wang)
Title: KC220053: Developing Clinically Relevant Genetic Mouse Models for Upper Track Urothelial Cancer

Effort: 1.20 calendar months (10%)

Supporting Agency: DOD-KCRP Concept

Grant Officer: Deanna Merendino, Grants Mgt Specialist
09/01/2023-08/31/2024

Performance Period:

Level of Funding:

Project Goals: The goal of this study is to develop clinically relevant UTUC GEMMs, which will facilitate basic and translational research.

Specific Aims: 1) Determine the impact of Arid1a/Pten/Trp53 knockout (KO) on urothelial tumor initiation, progression, and distant metastasis. 2) Determine the impact of nicotine and aristolochic acid on tumor progression in urothelium-specific Arid1a/Pten/Trp53 KO mice.

Principal Investigator

Role: None

Overlap:

(NEW)

Prostate Moon Shot (Logothetis, Aparicio, Navin)
Title: Prostate Moon Shot
Priority Project 3: Linking One-Carbon Metabolism to Lineage Promiscuity in Aggressive Variant Prostate Cancers (AVPC)

1.20 calendar months (10%)

Effort: MD Anderson Moon Shot Program

Supporting Agency: Carrie C. Feighl, 713-792-3477, Research_Finance@mdanderson.org

Grant Officer:

Performance Period:	09/01/2023-08/31/2024
Level of Funding:	
Project Goals:	
Specific Aims:	Our overall goal is to determine whether perturbations of the metabolic milieu impact candidate markers of lineage plasticity in AVPC tumors. 1) Determine the association between levels of SGOC pathway metabolites in mCRPC tumor biopsy samples, the AVPCm components, and outcomes in clinical trial participants treated with androgen signaling inhibitors (ASI) and chemotherapy (CTX). 2) Determine the association between levels of SGOC pathway metabolites, response to ASI and CTX in preclinical models, and markers of lineage promiscuity.
Role:	Co-Leader
Overlap:	None
RP220410	
Title:	<i>(Rai)</i> <i>Mechanisms and Therapies Focused on Epigenomic Alterations in Therapy-Resistant Prostate Cancers</i>
Effort:	1.20 calendar months (10% effort)
Supporting Agency:	CPRIT
Grants Officer:	Patty Moore
Performance Period:	03/01/2022-02/28/2025
Level of Funding:	
Project Goals:	
Specific Aims:	The overall goals of this proposal are to: 1) define functional driver enhancer elements that cause therapy resistance, 2) characterize AR, FOXA1, HOXB13, and SOX4 as core TFs mediating epigenome reprogramming, and 3) examine whether targeting enhancers using MLL/MENIN inhibitors alone or in combination with enzalutamide can be useful in suppressing growth of aggressive therapy-resistant prostate tumors in GEMMs for preclinical assessment. 1) To identify functional enhancer elements, their gene targets and downstream mechanism in specific epigenetic subtypes (EPIC). 2) To determine the molecular mechanism of EPIC-specific patterns of aberrant enhancer activation. 3) To determine the efficacy of BRD inhibition alone or in combination with pathway inhibitors for specific CMS subtypes.
Role:	Collaborator
Overlap:	None
(NEW)	
IRG	
Title:	<i>(Wang)</i> <i>The Role of DOPA Decarboxylase (DDC) in Regulating the Metabolic Reprogramming in NEPC and Resistance to Immune Checkpoint in Therapy</i>
Effort:	0.60 calendar months (5%)
Supporting Agency:	MD Anderson
Grant Officer:	—
Performance Period:	Carrie C. Feighl
Level of Funding:	09/01/2023-08/31/2025
Project Goals:	
Specific Aims:	The overall goal of this proposal is to establish DDC as a promising therapeutic target in NEPC and potentially repurpose DDC inhibitors, currently used for Parkinson's disease, to treat NEPC patients. 1) Determine the role of DDC-mediated metabolic reprogramming in the regulation of NEPC cells and T cells in vitro. 2) Determine the role of DDC in the regulation of NEPC progression in vivo.
Role:	Principal Investigator
Overlap:	None

(NEW)

RP230247

(Lin)

Title: *A Novel Combination Therapeutic Approach To Revitalizing Immunotherapy For Bone Metastatic Prostate Cancer*

Effort: 1.80 calendar months (15% effort)

Supporting Agency: CPRIT

Grants Officer: Patty Moore

Performance Period: 03/01/2023-02/28/2026

Level of Funding:

Project Goals: This study aims to develop a novel combination therapeutic approach to revitalize immunotherapy in bone metastatic prostate cancer. Prostate cancer bone metastasis is unique in that the bone lesions tend to be bone forming rather than bone lysing, which occurs in other cancers.

Specific Aims: 1) Determine the effects of tumor-induced bone formation on M2-like TAM recruitment and immune landscape of bone-TME in syngeneic mouse models. 2) Identify EC-OSB hybrid cell secreted factors (osteoclines) that promote the recruitment of M2-like TAM. 3) Develop strategies that target EC-OSB hybrid cells to improve immunotherapy outcomes for prostate cancer bone metastasis.

Role: Collaborator

Overlap: None

(NEW)

R01 CA276235-01

(Wang)

Title: *Cis-Aconitate Decarboxylase (ACOD1) in PMN-MDSC and Prostate Cancer Progression*

Effort: 1.80 calendar months (15% effort)

Supporting Agency: NIH/NCI

Grants Officer: Tiara L. Cleveland

Performance Period: 01/18/2023-12/31/2027

Level of Funding:

Project Goals: The major goal is to determine whether cis-aconitate decarboxylase (ACOD1) regulates the functions of polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) to promote prostate cancer progression and resistance to ICT.

Specific Aims: 1) Determine the role of ACOD1 in regulating the immunosuppressive activities of PMN-MDSCs. 2) Determine the role of ACOD1 in PMN-MDSCs in driving prostate cancer progression. 3) Determine whether Acod1 KO improves the response of prostate cancer to ICT.

Role: Principal Investigator

Overlap: None

PREVIOUS (Recently completed since the last report)

IRG

(Wang)

Title: *The Role of Acod1 in Polymorphonuclear Myeloid-Derived Suppressor Cells and Prostate Cancer Progression*

Effort: 1.20 calendar (10% effort)

Supporting Agency: Institutional Research Grant (IRG) MD Anderson

Grants Officer: Carrie C. Feigl

Performance Period: 12/17/2021-12/16/2022

Level of Funding:

Project Goals: The overall goal is to dissect the role of immunometabolism in prostate cancer progression and therapeutic resistance.

Specific Aims: 1) Elucidate the role of Acod1 in PMN-MDSCs and delineate the mechanisms by which Acod1 regulates PMN-MDSC functions. 2) determine the role of Acod1 in prostate cancer progression using preclinical models.

Role: Principal Investigator

Overlap: None

Prostate Moon Shot Title: (Logothetis/Aparicio/Navin)
Priority Project 2: Targeting Prostate Tumor-Induced Bone Formation to Reserve the Immunosuppressive Bone-TME and Improve the Efficacy of Immune Checkpoint Therapies

Effort: 0.60 calendar months (5% effort)

Grants Officer: Carrie C. Feighl

Performance Period: 09/01/2022-08/31/2023

Level of Funding:

Project Goals: The overall goal of this project is to determine whether inhibiting recruitment and activation of myeloid suppressor cells into the bone tumor microenvironment represents a therapeutic strategy to improve efficacy of immune checkpoint therapies in metastatic castrate-resistant prostate cancer.

Specific Aims: 1) Determine whether targeting the tumor-induced bone formation will modulate the accumulation of intratumoral immunosuppressive myeloid cells. 2) Determine whether targeting immunosuppressive myeloid cells in bone metastasis improves responses to ICTs.

Role: Collaborator

Overlap: None

CGC-FY22-02 Title: (Wang)
Delineate the Epigenetic/Transcriptional Programs in Driving Metastasis of Neuroendocrine Prostate Cancer (NEPC)

Effort: 0 calendar months

Supporting Agency: CPRIT-UTHealth

Grants Officer: Zhongming Zhao

Performance Period: 04/15/2022-04/14/2023

Level of Funding: (Award in the form of a credit for services)

Project Goals: This proposal aims to investigate the epigenetic and transcriptional regulation in the metastasis of NEPC, the most lethal subtype of prostate cancer.

Specific Aims: 1) Delineate the epigenetic and transcriptional reprogramming in NEPC metastasis. 2) Determine the role of KDM4A in NEPC metastasis in vivo and the underlying mechanisms.

Role: Principal Investigator

Overlap: None

APARICIO

CURRENT

(NEW)

N/A (Frigo)

Title: Targeting Arginine Metabolism to Treat Aggressive Variant Prostate Cancers

Time Commitments: 0.24 calendar months (2%)

Supporting Agency: Mike Slive Foundation

Grant Officer: Emily Capilouto

Performance Period: 01/01/2023-12/31/2023

Level of Funding:

Goals: To discover additional tumor characteristics that can improve the predictive value of the AVPC criteria and advise therapeutic interventions to improve clinical outcomes.

Specific Aims: 1) Determine the distribution of urea cycle enzymes across the AVPC tumor microenvironment. 2) Test the effects of ADI-PEG20 + carboplatin + cabazitaxel in preclinical models of AVPC.

Role: Co-PI

Overlap: None

NCT02703623

(Aparicio)
 Title: 2014-0386: A Dynamic Allocation Modular Sequential Trial of Approved and Promising Therapies in Men with Metastatic Castrate Resistant Prostate Cancer

Time Commitments: 0.12 calendar months (1%)
 Supporting Agency: Janssen Pharmaceuticals Inc.
 Grant Officer: Not available
 Performance Period: 05/03/2016-05/02/2024
 Level of Funding:
 Goal(s):

This randomized phase II trial studies the side effects and how well abiraterone acetate, prednisone, and apalutamide work with or without ipilimumab or cabazitaxel and carboplatin in treating patients with castration-resistant prostate cancer that has spread to other places in the body.

Specific Aims: 1) Estimate the overall survival (OS) of men with metastatic castration-resistant prostate cancer (mCRPC) who have satisfactory features after to 8 weeks of maximal androgen receptor (AR)-inhibitory therapy and receive treatment with abiraterone acetate, prednisone and apalutamide plus or minus ipilimumab. 2) Estimate the OS of men with mCRPC who have unsatisfactory features after to up to 8 weeks of maximal androgen receptor (AR)-inhibitory therapy and receive treatment with abiraterone acetate, prednisone, apalutamide, cabazitaxel and carboplatin. 3) Determine the toxicity profile of the following combinations in men with mCRPC: a. Abiraterone acetate, prednisone, apalutamide. b. Abiraterone acetate, prednisone, apalutamide and ipilimumab. c. Abiraterone acetate, prednisone, apalutamide, cabazitaxel and carboplatin. 4) Determine whether the baseline "AR response signature" correlates with satisfactory or unsatisfactory features after up to 8-weeks of treatment with abiraterone, prednisone and apalutamide.

Overlap: None

(NEW)

Bridge Funding

(Aparicio)
 Title: Effects of Arginine Depletion Combined with Platinum-Taxane Chemotherapy in Aggressive Variant Prostate Cancers (AVPC)

Time Commitments: 1.80 calendar months (15%)
 Supporting Agency: MD Anderson
 Grants Officer: Carrie C. Feigl
 Performance Period: 06/01/2023-05/31/2024
 Level of Funding:
 Goal(s):

Our overall goal is to arrive at rational, biologically-based combination therapies that effectively treat the aggressive variant prostate cancers (AVPC).

Specific Aims: 1) Determine the safety and efficacy of ADI-PEG20 combined with carboplatin+cabazitaxel chemotherapy (ADI-CC) in men with AVPC. 2) Determine the effects of ADI-CC on arginine metabolism and associated pathways in the AVPC TME, and their association with outcomes. 3) Determine the effects

	of ADI-CC on immune-cell populations and checkpoint expression in the AVPC TME.
Overlap:	None
<i>NCT03263650</i>	<i>(Aparicio)</i>
Title:	<i>2017-0133: Randomized Phase II Study of Olaparib Maintenance Following Cabazitaxel-Carboplatin Induction Chemotherapy in Men with Aggressive Variant Prostate Cancer (AVPC)</i>
Time Commitments:	0.12 calendar months (1%)
Supporting Agency:	Astra Zeneca
Grants Officer:	Gayle Ewing
Performance Period:	08/15/2017-08/14/2024
Level of Funding:	
Goal(s):	The goal of this clinical research study is to learn if olaparib, when given after treatment with cabazitaxel, carboplatin, and prednisone, can help to control aggressive variant prostate cancer (AVPC). The safety of these drugs will also be studied.
Specific Aims:	N/A
Overlap:	None
<i>W81XWH-20-1-0257</i>	<i>(Aparicio)</i>
Title:	<i>PC190353: Chemoimmunotherapy for Aggressive Variant Prostate Cancers (AVPC)</i>
Time Commitments:	1.20 calendar months (10%)
Supporting Agency:	DOD
Grants Officer:	Kenneth E. Grenier
Performance Period:	09/01/2020-08/31/2024
Level of Funding:	
Goal(s):	Our overall goal is to arrive at biologically-based rational combinations to treat the AVPC with curative intent.
Specific Aims:	1) Determine the effect of durvalumab on the clinical efficacy of cabazitaxel-carboplatin induction and olaparib maintenance in men with AVPC. 2) Determine the effects of durvalumab on the immune components of the tumor microenvironment when added to cabazitaxel-carboplatin induction and to olaparib maintenance in men with AVPC.
Overlap:	None
(NEW)	
<i>Prostate Moon Shot</i>	<i>(Logothetis, Aparicio, Navin)</i>
Title:	<i>Prostate Cancer Moon Shot. Priority Project 3: Linking One-Carbon Metabolism to Lineage Promiscuity in Aggressive Variant Prostate Cancers (AVPC).</i>
Time Commitments:	1.20 calendar months (10%)
Supporting Agency:	MD Anderson
Grants Officer:	Carrie C. Feighl
Performance Period:	09/01/2023-08/31/2024
Level of Funding:	
Goal(s):	Our overall goal is to determine whether perturbations of the metabolic milieu impact candidate markers of lineage plasticity in AVPC tumors.
Specific Aims:	1) Determine the association between levels of SGOC pathway metabolites in mCRPC tumor biopsy samples, the AVPCm components, and outcomes in clinical trial participants treated with androgen signaling inhibitors (ASI) and chemotherapy (CTX). 2) Determine the association between levels of SGOC

Overlap:	pathway metabolites, response to ASI and CTX in preclinical models, and markers of lineage promiscuity. None
(THIS AWARD)	
<i>W81XWH-21-1-0522</i>	<i>(Wang)</i>
Title:	<i>PC200420: Targeting Histone Lysine Demethylase KDM4A in Neuroendocrine Prostate Cancer</i>
Time Commitments:	0.60 calendar months (5%)
Supporting Agency:	DOD
Grants Officer:	Kimberly Carter
Performance Period:	09/01/2021-08/31/2024
Level of Funding:	
Goal(s):	
Specific Aims:	Our overall goal is to develop combination therapy to improve the clinical outcome of platinum-taxane chemotherapy in patients with NEPC. 1) Determine the role of KDM4A in NEPC progression using organoids, PDXs, and GEMMs. 2) Examine the mechanism(s) by which KDM4A regulates UPR signaling. 3) Determine whether KDM4 inhibitors improve the therapeutic outcomes of platinum-taxane chemotherapy in NEPC.
Role:	Co-Investigator
Overlap:	None
(NEW)	
<i>22CHAL09</i>	
Title:	
Time Commitments:	<i>(Zhao)</i>
Supporting Agency:	<i>Targeting B7-H3 in Aggressive Variant Prostate Cancer</i>
Grant Officer:	1.20 calendar months (10%)
Performance Period:	Prostate Cancer Foundation – Challenge Award
Level of Funding:	Audrey Gardner
Goal(s):	01/23/2023-01/22/2025
Specific Aims:	Our overall goal is to determine the therapeutic potential of DS-7300, a B7-H3-targeting antibody-drug conjugate (ADC) warheaded with a novel DNA topoisomerase inhibitor, in men with AVPC. 1) Determine the differential expression patterns of B7-H3 in molecularly defined mCRPC subsets. 2) Determine regulatory mechanisms of B7-H3 expression by AVPC molecular profile in mCRPC. 3) Evaluate the efficacy of DS-7300 in preclinical models of AVPC.
Role:	Co-PI
Overlap:	None
(NEW)	
<i>W81XWH-22-1-0259</i>	
Title:	
Time Commitments:	<i>(Aparicio)</i>
Supporting Agency:	<i>PC210079P1: An Integrated Genomic Definition and Therapeutic Strategy for Androgen Indifferent Prostate Cancers</i>
Grant Officer:	1.80 calendar months (15%)
Performance Period:	DOD
Level of Funding:	Michelle L. Cromwell
Goal(s):	09/30/2022-09/29/2025
	To develop statistical methods and tools to further the genomic analysis of heterogeneous tumor samples.

Specific Aims: 1) To develop and validate compartment-specific plasticity scores using integrative deconvolution of bulk genomic and transcriptomic signatures. 2) To determine the association between the plasticity scores, clinical outcomes and clinically available biomarker signatures.

Role: Partnering PI

Overlap: None

(NEW)

R01 CA275990-01 (Zhao)
 Title: *Novel Approaches Targeting B7-H3 in Castration-Resistant Prostate Cancer*
 Time Commitments: 0.60 calendar months (5%)
 Supporting Agency: NIH/NCI
 Grant Officer: Justin Birken
 Performance Period: 01/01/2023-12/31/2027
 Level of Funding:
 Goal(s): The overall objective of this application is to elucidate the complex role of B7-H3 signaling in prostate cancer as well as develop biomarker-driven B7-H3 targeted therapy for castration-resistant prostate cancer.

Specific Aims: 1) Elucidate B7-H3's impact on progression of prostate cancer containing PTEN/TP53 loss, 2) Understand how B7-H3 signaling modulates immunosuppressive myeloid cells in CRPC.

Role: Co-Investigator

Overlap: None

NCT04702737 (Aparicio)
 Title: *2021-0108: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of Delta-like Protein 3 Half-life Extended Bispecific T-cell Engager AMG 757 in Subjects with De Novo or Treatment Emergent Neuroendocrine Prostate Cancer*
 Time Commitments: 0.12 calendar months (1%)
 Supporting Agency: Amgen Inc.
 Grant Officer: Shani Hilliard,
 Performance Period: 11/01/2021-10/31/2028
 Level of Funding:
 Goal(s): The overall goal of this study is to evaluate the safety and tolerability of Tarlatamab and will determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D).

Aims: N/A

Overlap: None

(NEW)

NCT04428788 (Aparicio)
 Title: *2022-0612: A Phase 1, Multi-Center, Open-Label, Dose-Finding Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Of Cc-94676 in Subjects with Metastatic Castration-Resistant Prostate Cancer*
 Time Commitments: 0.12 calendar months (1%)
 Supporting Agency: Bristol-Myers Squibb/Celgene
 Grants Officer: Jennifer Walsh
 Performance Period: 12/15/2022-12/14/2029
 Level of Funding:

Goal(s): The purpose of this study is to assess the safety, tolerability and preliminary efficacy of CC-94676 in men with progressive metastatic castration resistant prostate cancer.

Aims: Primary Objectives: 1) Determine the safety and tolerability of CC-94676. 2) Define the non-tolerated dose (NTD), the maximum tolerated dose (MTD), and/or the recommended Phase 2 dose (RP2D) of CC-94676. Secondary Objectives: 1) Provide information on the preliminary efficacy of CC-94676. 2) Characterize the pharmacokinetics (PK) of CC-94676 in plasma.

Overlap: None

PREVIOUS (Recently completed since last report)

P50 CA140388-10 (Logothetis/Thompson)
 Title: *MD Anderson Cancer Center Prostate Cancer SPORE Project 1: Integrating Ipilimumab Immunotherapy with Approved Treatment Strategies in CRPC*

Time Commitments: 0.36 calendar months (3% effort)
 Supporting Agency: NIH/NCI
 Grants Officer: Ashley Salo
 Performance Period: 09/01/2016-08/31/2023 NCE
 Level of Funding:
 Goal(s): To rationally integrate anti-CTLA-4 (ipilimumab) immunotherapy with agents targeting the AR signaling pathway to provide durable clinical benefit with improved survival in patients with prostate cancer, and utilize novel imaging techniques to accurately identify tumor responses.

Specific Aims: 1) Identify biological changes indicative of mechanistic pathways that contribute to clinical outcomes in matched tumor and blood specimens obtained from prostate cancer patients given drugs targeting the AR signaling pathway plus anti-CTLA-4 immunotherapy. 2) Determine clinical outcomes after treatment with AR-targeting agents (ARN-509 + abiraterone acetate) followed by concurrent anti-CTLA-4 immunotherapy and prospectively evaluate the effectiveness of selected biological pathways identified in Aim 1 to be indicative of mechanistic pathways that contribute to clinical outcomes. 3) Determine the efficacy of targeting B7-H3 and B7-H4 with radiolabeled monoclonal antibodies as a non-invasive means to detect prostate cancer.

Role:
 Overlap: Co-Investigator, Project 1
 None

NCT04388852 (Aparicio)
 Title: *2019-0967: DS3201 With Ipilimumab in Patients with Metastatic Aggressive Variant Prostate (AVPC), Urothelial (UC), and Renal Cell (RCC) Carcinomas*

Time Commitments: 0 calendar months
 Supporting Agency: MD Anderson
 Performance Period: 03/18/2020-no end date (End date will be when study is completed)
 Level of Funding:
 Goal(s): This phase Ib trial studies the side effects and best dose of DS3201 when given together with and ipilimumab for the treatment of patients with prostate, urothelial, or renal cell cancer that has spread to other places in the body (metastatic). *Primary objectives:* 1) Determine the maximum tolerated dose (MTD) and confirm the safety and tolerability of valemestostat (DS3201) given in combination with ipilimumab in patients with metastatic AVPC, UC, and RCC. 2) Screen for associations between changes in the tumor microenvironment and clinical outcomes. *Secondary objectives:* 1) Assess the immunologic and molecular effects

Aims:

on tissue samples of participants treated with DS3201 in combination with ipilimumab in patients with metastatic AVPC, UC and RCC. 2) Estimate the time to treatment failure (TTF) of patients with metastatic AVPC, UC and RCC treated with DS3201 in combination with ipilimumab. 3) Estimate the overall response rate (ORR) of patients with metastatic AVPC, UC and RCC treated with DS3201 in combination with ipilimumab.

Overlap: None

LEE, Min Gyu

CURRENT

RCTS2021-00059811-Y1 (MG Lee)

Title: *Internal Funding*

Time Commitments: 0 calendar months

Supporting Agency: MD Anderson

Grants Officer: Research_Finance@mdanderson.org

Performance Period: 06/01/2021-05/31/2023

Level of Funding:

Goal(s): The objective of this internal funding is to provide financial support for the re-submission of the R01 application (R01 CA262324-01A1) that is designed to define the oncogenic role of heterozygous loss of Kmt2d in medulloblastoma pathogenesis. This fund can be used to support salaries of trainees and technicians, laboratory operating supplies and laboratory maintenance but does not allow salary support of tenured/tenure-track faculty.

Specific Aims: N/A

Role: Principal Investigator

Overlap: None

(THIS AWARD)

W81XWH-21-1-0522

Title: *(Wang)*
PC200420: Targeting Histone Lysine Demethylase KDM4A in Neuroendocrine Prostate Cancer

Time Commitments: 0.60 calendar months (5% effort)

Supporting Agency: DOD

Grants Officer: Kimberly Carter

Performance Period: 09/01/2021-08/31/2024

Level of Funding:

Goal(s): Our overall goal is to develop combination therapy to improve the clinical outcome of platinum-taxane chemotherapy in patients with NEPC.

Specific Aims: 1) Determine the role of KDM4A in NEPC progression using organoids, PDXs, and GEMMs. 2) Examine the mechanism(s) by which KDM4A regulates UPR signaling. 3) Determine whether KDM4 inhibitors improve the therapeutic outcomes of platinum-taxane chemotherapy in NEPC.

Role: Co-Investigator

Overlap: None

R01 CA193297-06 *(Jae-II Park)*

Title: *PAF- Remodeled DREAM Complex in Cancer and Regeneration*

Time Commitments: 0.24 calendar months (2% effort)

Supporting Agency: NIH/NCI

Grants Officer: Manda C Richards

Performance Period: 07/01/2020-06/30/2025

Level of Funding: \$1,791,473

Goal(s): The major goals of this project are to understand the mechanism of cell quiescence exit for tumor initiation and tissue regeneration.

Specific Aims: 1) Decipher the molecular mechanism of the PAF-remodeled DREAM complex. 2) Determine the pathological and physiological roles of PAF and PAF-expressing cells in lung cancer and lung regeneration.

Role: Co-Investigator

Overlap: None

R01 CA262324-01A1 (Lee)
Title: Heterozygous KMT2D Loss and Medulloblastoma
 Time Commitments: 2.40 calendar months (20% effort)
 Supporting Agency: NIH/NCI
 Grants Officer: Nailah Iman Shaw, 240-276-7311, nailah.shaw@nih.gov
 Performance Period: 08/09/2022-07/31/2027
 Level of Funding: \$2,201,960
 Goal(s): The goals of this project are to determine the oncogenic role of heterozygous loss of *Kmt2d* in medulloblastoma (MB) pathogenesis.
 Specific Aims: 1) Characterize the MB-promoting effect of heterozygous *Kmt2d* loss using genetically engineered mouse models. 2) Define the molecular mechanism by which heterozygous *Kmt2d* loss promotes MB. 3) Determine how heterozygous *Kmt2d* loss causes epigenomic alterations.
 Role: Principal Investigator
 Overlap: None

PREVIOUS (Recently completed since last report)

R01 CA207109-05 (MG Lee)
Title: Role of the Histone Methyltransferase MLL4 in Medulloblastoma
 Time Commitments: 1.80 calendar months (15% effort)
 Supporting Agency: NIH/NCI
 Grants Officer: Elizabeth Bui, 240-276-6323, mimi.bui@nih.gov
 Performance Period: 06/07/2017-05/31/2023 (NCE)
 Level of Funding: \$1,886,478
 Goal(s): The major goals of this project are to define the role of the histone methyltransferase MLL4 in regulating medulloblastoma (MB).
 Specific Aims: 1) Assess the role of MLL4 in MB development using genetically engineered mouse models. 2) Determine the molecular mechanism underlying the genesis of Mll4-loss-driven MB. 3) Characterize the effect of Mll4 loss on epigenetic signatures (super-enhancers/enhancers, broad H3K4me3, and bivalency) during MB genesis.
 Role: Principal Investigator
 Overlap: None

R01 CA207098-05 (MG Lee)
Title: Role of the Histone Modifier KDM2A in Lung Cancer
 Time Commitments: 1.20 calendar months (10% effort)
 Supporting Agency: NIH/NCI
 Grants Officer: Renee Carruthers, 301-631-3018, carruthersr@mail.nih.gov
 Performance Period: 08/01/2017-07/31/2023 (NCE)
 Level of Funding:
 Goal(s): The major goals of this project are to define the role of the histone modifier KDM2A in lung tumorigenicity

Specific Aims: 1) Determine the role of the KDM2A-associated protein HP1y in KDM2A-mediated gene repression. 2) Gain greater insight into the molecular mechanisms by which KDM2A promotes tumorigenicity of NSCLC cells. 3) Assess the in vivo role of KDM2A in lung tumorigenesis and metastasis using genetically engineered mouse models.

Role: Principal Investigator

Overlap: None

ZHANG, Miao

CURRENT

(THIS AWARD)

W81XWH-21-1-0522

Title:

(Wang)

PC200420: Targeting Histone Lysine Demethylase KDM4A in Neuroendocrine Prostate Cancer

Time Commitments: 0.36 calendar months (3%), Year 3

Supporting Agency: DOD

Grants Officer: Kimberly Carter

Performance Period: 09/01/2021-08/31/2024

Level of Funding:

Goal(s): Our overall goal is to develop combination therapy to improve the clinical outcome of platinum-taxane chemotherapy in patients with NEPC.

Specific Aims: 1) Determine the role of KDM4A in NEPC progression using organoids, PDXs, and GEMMs. 2) Examine the mechanism(s) by which KDM4A regulates UPR signaling. 3) Determine whether KDM4 inhibitors improve the therapeutic outcomes of platinum-taxane chemotherapy in NEPC.

Role: Co-Investigator

Overlap: None

(NEW)

W81XWH-20-1-0257

Title:

(Aparicio)

PC190353: Chemoimmunotherapy for Aggressive Variant Prostate Cancers (AVPC)

Time Commitments: 1.20 calendar months (10%)

Supporting Agency: DOD

Grants Officer: Kenneth E. Grenier

Performance Period: 09/01/2020-08/31/2024

Level of Funding:

Goal(s): Our overall goal is to arrive at biologically-based rational combinations to treat the AVPC with curative intent.

Specific Aims: 1) Determine the effect of durvalumab on the clinical efficacy of cabazitaxel-carboplatin induction and olaparib maintenance in men with AVPC. 2) Determine the effects of durvalumab on the immune components of the tumor microenvironment when added to cabazitaxel-carboplatin induction and to olaparib maintenance in men with AVPC.

Role: Co-Investigator

Overlap: None

(NEW)

RP220410

Title:

(Rai)

Mechanisms and Therapies Focused on Epigenomic Alterations in Therapy-Resistant Prostate Cancers

Time Commitments: 0.24 calendar months (2%)

Supporting Agency:	CPRIT
Grant Officer:	Patty Moore,
Performance Period:	03/01/2022-02/28/2025
Level of Funding:	
Goal(s):	The overall goals of this proposal are to define functional driver enhancer elements that cause therapy resistance, characterize AR, FOXA1, HOXB13, and SOX4 as core TFs mediating epigenome reprogramming, and examine whether targeting enhancers using MLL/MENIN inhibitors alone or in combination with enzalutamide can be useful in suppressing growth of aggressive therapy-resistant prostate tumors in GEMMs for preclinical assessment.
Specific Aims:	1) To identify functional enhancer elements, their gene targets and downstream mechanism in specific epigenetic subtypes (EPIC). 2) To determine the molecular mechanism of EPIC-specific patterns of aberrant enhancer activation. 3) To determine the efficacy of BRD inhibition alone or in combination with pathway inhibitors for specific CMS subtypes.
Role:	Collaborator
Overlap:	None

(NEW)

<i>W81XWH-22-1-0188</i>	<i>(Zurita)</i>
Title:	<i>PC210046P1: Revisiting Antiangiogenic Therapy to Target Prostate Cancer Metabolism</i>
Time Commitments:	0.12 calendar months (1%)
Supporting Agency:	DOD
Grant Officer:	Joshua McKean
Performance Period:	09/01/2022-08/31/2025
Level of Funding:	
Goal(s):	The goal of this proposal is to evaluate whether co-targeting cancer cell anaplerotic metabolism and angiogenesis can synergize to treat advanced prostate cancer.
Specific Aims:	1) Evaluate angiogenesis as a mechanism of resistance to CAMKK2 inhibition and anaplerotic stress. 2) Determine if a clinical-grade inducer of anaplerotic stress sensitizes advanced prostate cancers to the antitumor effects of antiangiogenic therapy. 3) Assess whether anaplerotic signaling predicts sensitivity to antiangiogenic therapy in patients.
Role:	Collaborator
Overlap:	None

(NEW)

<i>R01 CA275138-01A1</i>	<i>(Frigo/Zurita)</i>
Title:	<i>Revisiting Antiangiogenetic Therapy to Target Prostate Cancer Metabolism</i>
Time Commitments:	0.24 calendar months (2%)
Supporting Agency:	NIH/NCI
Grant Officer:	Joy Kearse
Performance Period:	05/12/2023-04/30/2028
Level of Funding:	
Goal(s):	To evaluate whether co-targeting cancer cell anaplerotic metabolism and tumor angiogenesis can synergize to treat hormone-sensitive prostate cancer, and to determine whether biomarkers of anaplerotic signaling can predict response to antiangiogenic therapy and therefore, guide patient selection.
Specific Aims:	1) Evaluate angiogenesis as a mechanism of resistance to CAMKK2 inhibition and anaplerotic stress. 2) Determine if a clinical-grade inducer of anaplerotic stress sensitizes advanced prostate cancers to the antitumor effects of antiangiogenic

therapy. 3) Assess whether anaplerotic signaling predicts sensitivity to antiangiogenic therapy in patients.

Role: Co-Investigator
Overlap: None

I, PD/PI or other senior/key personnel confirm that I:

- Certify that the current and pending support provided on the application is current, accurate and complete;
- Agree to update such disclosure at the request of the agency prior to the award of support and at any subsequent time the agency determines appropriate during the term of the award; and
- Have been made aware of the requirements under Section 223(a)(1) of this Act.²⁸ DOD General Application Instructions 18

False, fictitious, or fraudulent statements or claims may result in criminal, civil, or administrative penalties (U.S. Code, Title 18, Section 1001)

What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

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.

Provide the following information for each partnership:

Organization Name:

Location of Organization: (if foreign location list country)

Partner's contribution to the project (identify one or more)

- Financial support;
- In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);
- Facilities (e.g., project staff use the partner's facilities for project activities);
- Collaboration (e.g., partner's staff work with project staff on the project);
- Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and
- Other.

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ebrap.org> for each unique award.*

Nothing to report

QUAD CHARTS: *If applicable, the Quad Chart (available on <https://www.usamraa.army.mil/Pages/Resources.aspx>) should be updated and submitted with attachments.*

Not applicable

- 9. APPENDICES:** *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc. Reminder: Pages shall be consecutively numbered throughout the report. DO NOT RENUMBER PAGES IN THE APPENDICES.*

Not applicable