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TITLE: Targeting Histone Lysine Demethylase KDM4A in Neuroendocrine Prostate Cancer

PRINCIPAL INVESTIGATOR: Guocan Wang, Ph.D.

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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PC200420 ANNUAL REPORT

September 1, 2021 – August 31, 2022

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% completed 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% completed 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% completed
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% completed
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	50% completed. Will continue in the next year

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	
Milestone(s) Achieved: establishing a key functional role for KDM4A in NEPC progression in organoid models	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	50% completed. Will continue in the next year
Subtask 2: Histopathological analysis of KT & TRAMP mice Tumor will be subjected to histopathological analysis	4-25	30% completed. It will be continued in the next year.
Milestone(s) Achieved: establishing a key functional role for KDM4A in NEPC progression in cKO model	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% completed
Subtask 2: Perform ChIP-qPCR of KDM4A and histone modifications in NEPC cells Perform ChIP-qPCR in NEPC cell lines	4-8	0% completed because we were able to generate high quality of ChIP-seq data from Subtask 3
Subtask 3: Perform ChIP-seq analysis of KDM4A and Histone modification in NEPC cells. ChIP-seq to identify KDM4A target genes	9-14	70% completed. It will be continued in the next year.
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	80% complete. It will be continued in the next year.
Milestone(s) Achieved: establishing ATF3, DDIT3,c-JUN as KDM4A target genes & identifying other KDM4A target genes	13	
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	50% complete. It will be continued in the next year.
Subtask 2: Examine ER stress response in cell lines *in vitro* ER stress response and UPR signaling will be analyzed by western blot and qPCR in NEPC and ARPC cell lines	1-13	70% complete. It will be continued in the next year.

Milestone(s) Achieved: establishing a role for KDM4A in ER stress and UPR signaling	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. *Source of biospecimens:* 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	
Subtask 3: IHC staining of human prostate tumor tissues for ER stress markers and KMD4A Tumors from above will be stained by IHC	19-28	
Subtask 5: Analyze IHC staining results IHC staining data from above will be analyzed	29-36	
Milestone(s) Achieved: characterization of KDM4A expression and UPR signaling in human tumor samples	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, CTBX (120 male NEPC GEMMs generated in Wang lab)	11-28	20% 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	
Milestone(s) Achieved: establishing the efficacy of KDM4 inhibitor combination therapy in GEMMs	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, CTBX (240 male SCID mice, Jackson Lab)	11-28	20% 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	
Milestone(s) Achieved: establishing the efficacy of KDM4 inhibitor combination therapy in PDXs	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

a) Seeking approval from Local institutional animal care and use committee (IACUC), USAMRDC Animal Care and Use Review Office (ACURO), local institutional review board (IRB), and USAMRDC Human Research Protection Office (HRPO).
b) Establishing key models, including organoids (MSK-PCa-4), PDXs (MDA PCa 144-13 and MDA PCa 155 obtained from Dr. Nora Navone), and GEMMs [Pb-Cre4;Kdm4a$^{fl/fl}$;TRAMP (KT) mice and TRAMP] for proposed studies.
c) Validating key reagents (e.g., antibodies) for use in mechanistic studies and performing pilot experiments to determine the proper dose of carboplatin used for combination therapy.
d) Performing functional and mechanistic studies to delineate the function of KDM4A *in vitro* and *in vivo* using cell lines, organoids, PDXs, and GEMMs.
e) Initiating experiments to determine the efficacy of KDM4 inhibitor QC6352 in NEPC as monotherapy and combination.

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

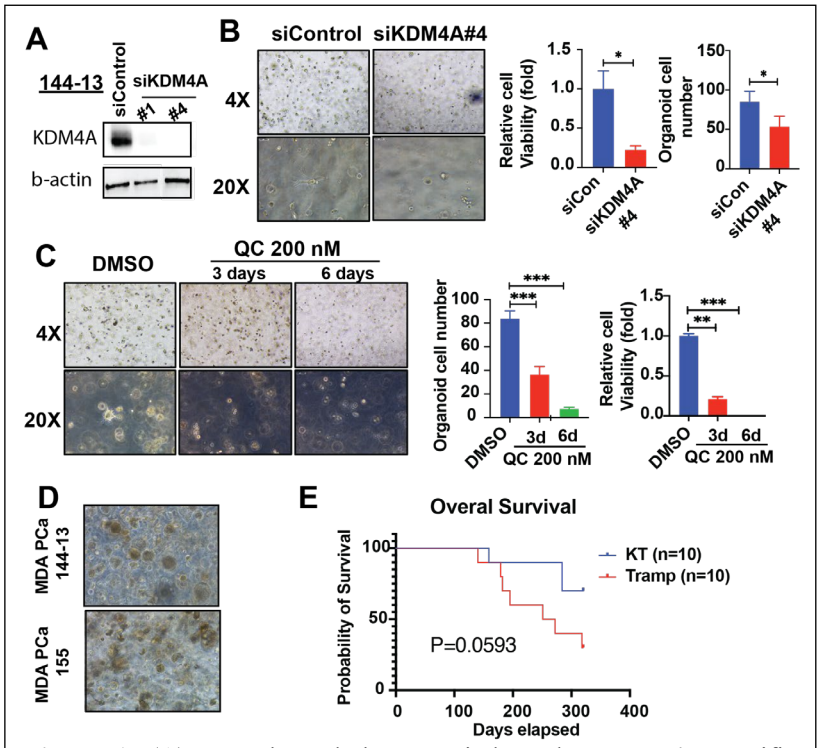

Figure 1. (**A**) WB showed that two independent KDM4A-specific siRNAs efficiently knocked down KDM4A expression in 144-13 cells. (**B-C**) KDM4A KD (6 days) or KDM4i (QC6352) treatment (3 & 6 days) led to a significant reduction in the number and viability of MKS-PCa4 organoids. (**D**) Organoids were generated from MDA PCa 144-13 and MDA PCa 155 PDXs. (**E**) Kapan Meier survival curve of KT and TRAMP mice [n=10, Log-rank (Mantel-Cox) test].

Aim 1. (**a**) *Establishment of PDXs lines in mice*. In order to utilize the NEPC PDXs for our studies, we have obtained MDA PCa 144-13 and MDA PCa 155 PDXs from Dr. Nora Navone and successfully generated tumors in SCID mice. (**b**) *KDM4A knockdown (KD) or inhibition suppressed the growth of MSK-PCa4 organoid in vitro*. To determine whether KDM4A plays an important role in the growth of NEPC organoids *in vitro*, we first validated the KD efficiency of KDM4A-specific siRNAs in 144-13 cells using Western blot (WB) (**Figure 1A**). We then transfected a validated KDM4A-specific siRNA with high KD efficiency into MSK-PCa4. We found that KDM4A KD led to a dramatic reduction in the number of organoids and reduced cell viability (**Figure 1B**). Treatment of MSK-PCa4 organoids with KDM4 inhibitor (KDM4i) QC6352 (200 nM) similarly led to a significant reduction in the number of organoids and reduced cell viability (**Figure 1C**). (**c**) *Establishing PDX-derived organoids*. We were able to generate organoids from MDA PCa 144-13 and MDA PCa 155 PDXs (**Figure 1D**). (**d**) *Kdm4a KO*

reduced the tumor burden in GEMMs. We have generated 10 Pb-Cre4;KDM4A$^{fl/fl}$;TRAMP (KT) mice and 10 TRAMP mice for survival analysis & 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 an increase in the median survival of KT mice compared to TRAMP mice, although it has not reached statistical significance (**Figure 1E**).

Aim 2: (**a**) *Validating antibodies for ChIP analysis*. We used a KDM4A-specific antibody suitable for ChIP-seq (provided by Dr. Roland Schüle, Universität Freiburg, Germany). We confirmed its high efficiency in immunoprecipitation (IP) of KDM4A in human NEPC cell line 144-13, followed by Western blot (WB) (**Figure 2A**). (**b**) *ChIP-seq in NEPC cells*. To determine whether KDM4A directly regulates ATF3, DDIT3, and c-JUN transcription and also delineate the epigenetic landscape regulated by KDM4A, we performed ChIP-seq using antibodies for KDM4A, H3K9me3, H3K36me3, H3K27ac, and CTCF in NEPC cell line 144-13. H3K9me3 and H3K36me3 are KDM4A substrates. H3K27ac marks active promoters and enhancers. CTCF is a mediator of chromatin looping and TAD boundary insulator. The data is currently being analyzed by Dr. Jianhua Zhang. Our preliminary analyses found that KDM4A mainly binds to promoter/transcription factor starting sites (TSS) (**Figure 2B**). We also examined the histone marks and CTCF binding around KDM4A peaks. We found that K3K9me3 and H3K36me3 were less abundant at loci close to KDM4A peaks than those distant from the KDM4A peaks (~1-1.5kb) (**Figure 2C**), consistent with the role of KDM4A in the demethylation of H3K9me3 and H3K36me3. Importantly, we found that KDM4A binds to the ATF3 promoter, which is marked by prominent H3K27ac (**Figure 2D**). KDM4A also binds broadly to JUN locus and its binding overlapped with the H3K27ac signal (**Figure 2E**). However, KDM4A does not appear to bind to the promoter/enhancer of DDIT3 (**Figure 2F**). The promoter of ATF3 and the promoter/gene body of JUN lacks H3K9me3 but has abundant H3K36me3 signal, suggesting that KDM4A actively demethylates H3K9me3 but not H3K36me3 at the genomic loci of *ATF3* and *JUN* (**Figure 2D-E**). (**c**) *Analyzing publicly available and in-house microarray, RNA-seq, ChIP-seq of human and mouse NEPC*. To delineate the mechanism by which KDM4A regulates tumor progression, we analyzed publicly available RNA-seq (GSE95293: KDM4i vs control in TNBC) and in house RNA-seq datasets (PTR cells with Kdm4a KD and control cells) and ChIP-seq data (GSE95190) in triple-negative breast cancer (TNBC). We first compared the effects of KDM4 inhibitor and *Kdm4a* KD on gene expression. Differentially expressed genes (DEGs) were identified in TBNC (KDM4i vs DMSO) and PTR (Kdm4a KD vs control (**Figure 3A-B**). Interestingly, only a small

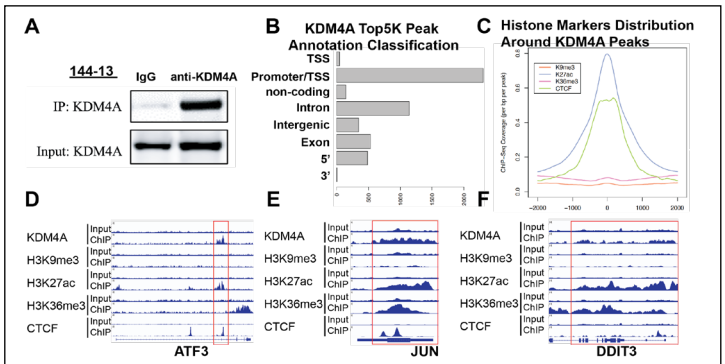

Figure 2. (**A**) Western blot showed that a KDM4A-specific antibody efficiently pulled down KDM4A in 144-13 cells. (**B**) The distribution of KDM4A binding peaks in the 144-13 ChIP-seq showed that KDM4A mainly binds to promoter/TSS. (**C**) The histone mark distribution around the KDM4A binding peaks. (**D-F**) ChIP-seq of KDM4A, H3K9me3, H3K27ac, H3K36me3, and CTCF at ATF3, JUN, and DDIT3 loci.

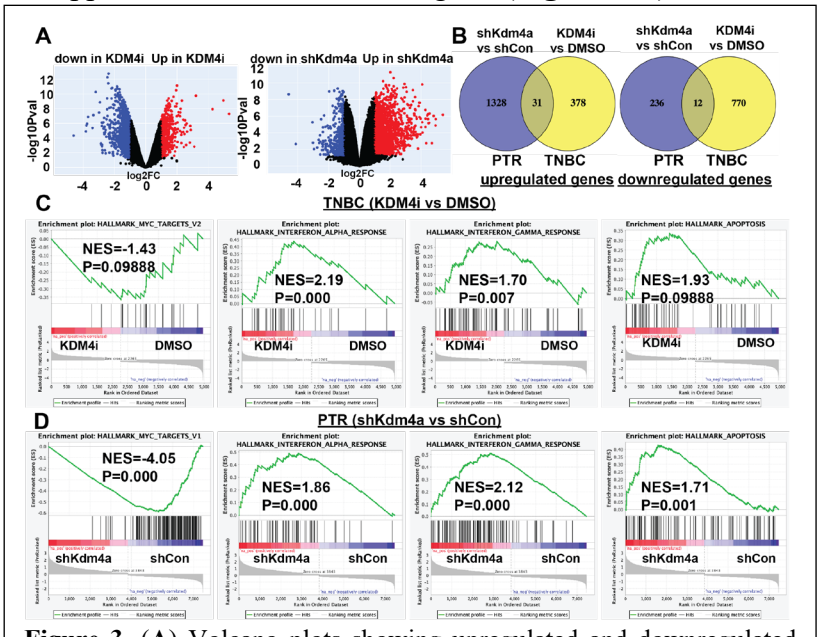

Figure 3. (**A**) Volcano plots showing upregulated and downregulated genes in KDM4i-treated TNBC and Kdm4a-KD PTR cells. (**B**) Venn diagram showing genes that are either upregulated or downregulated in both KDM4i-treated TNBC and Kdm4a-KD PTR cells. (**C-D**) GSEA analysis of RNA-seq analysis on TNBC (KDM4i vs DMSO) and PTR cells (shKdm4a vs shControl) identified MYC, interferon alpha and gamma, and apoptosis as common hallmarks.

subset of genes is commonly downregulated or upregulated in KDM4i-treated TNBC and shKdm4a-PTR cells (fold change ≥2 or ≤-2 (**Figure 3B**). However, we identified several common pathways that are downregulated and upregulated in KDM4i-treated TNBC and shKdm4a-PTR cells, including MYC, interferon alpha and gamma signaling, and apoptosis as shown by gene set enrichment analysis (GSEA) (**Figure 3C-D**). Together, these data suggest that KDM4A regulates common pathways across different cancer types, despite cancer type-specific gene expression regulated by KDM4A. (**d**) *Examining ER stress response in cell lines in vitro*. We first compared the response of 144-13, a well-established NEPC cell line, and LNCaP, a well-established prostate adenocarcinoma cell line, to tunicamycin (Tn), a potent ER stress inducer. We found that DDIT3 and phospho-c-JUN, two markers for ER stress and UPR were more profoundly induced by Tn in 144-13 cells than in LNCaP cells (**Figure 4A**). Interestingly, Tn induced apoptosis as shown by cleaved caspase 3 in 144-13 cells but not in LNCaP cells (**Figure 4A**), suggesting that 144-13 cells may be more sensitive to ER stress-induced cell death. We then analyzed the effect QC6352 on ER stress response and UPR signaling by Western blot (WB) in PSTR and PTR cells. As expected, DDIT3, a key marker for ER stress and UPR, was induced by two well-established ER stress inducers, tunicamycin (Tn) and thapsigargin (Tg) (**Figure 4B**). We found that QC6352 also induced the expression of DDIT3 (**Figure 4B**). We then examined the effect of *Kdm4a* KD on the ER stress and UPR in PSTR cells. We found that *Kdm4a* KD led to a reduction in the induction of MYC, phospho-c-JUN, JUN, ATF3, and ATF4 by Tn treatment compared to the control cells treated with Tn (**Figure 4C**). Also, we examined the effect of KDM4A overexpression (OE) on ER stress and UPR in *Kdm4a*-KO PSTR cells. We found that KDM4A OE led to reduced expression of DDIT3, cleaved PARP, and cleaved caspase 3, and increased expression of c-Jun and phosphor-c-JUN (**Figure 4D**). (**e**) *Validating antibodies for proteins in UPR signaling*. We have performed IHC staining to test multiple key proteins involved in ER stress and UPR signaling, including (BiP, P4HB, phospho-eIF2α, phospho-JNK) on mouse prostate adenocarcinoma (Pb-Cre;**P**ten$^{fl/fl}$;**S**mad4$^{fl/fl}$, aka PS model) and NEPC (Pb-Cre;**P**ten$^{fl/fl}$;**T**rp53$^{fl/fl}$;**R**b1$^{fl/fl}$, aka PTR model). We found that NEPC has increased expression of these proteins (**Figure 4E**).

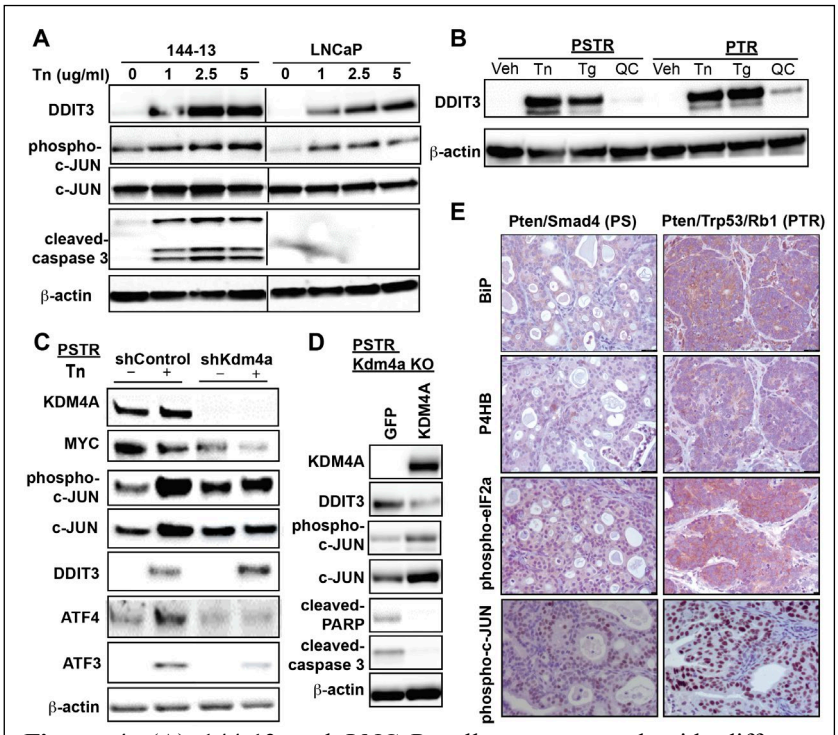

Figure 4. (**A**) 144-13 and LNCaP cells were treated with different concentrations of Tn for 24 hrs. WB was used to analyze the expression f DDIT3, phospho-c-JUN, cleaved caspase 3 and b-actin. (**B**) A low dose of QC (500 nM) induced DDIT3 expression in PSTR and PTR cells. Tn (2.5 μg/ml) and Tg (5 μM) were used as positive control. (**C**) *Kdm4a* KD in PSTR cells led to a higher level of DDIT3, and reduced levels of MYC, phospho-c-JUN, c-JUN, ATF4, and ATF3 when they were treated with Tn compared to control cells treated with Tn (2.5 μg/ml). (**D**) KDM4A overexpression in PSTR KO cells suppressed the expression of DDIT3, cleaved PARP, and cleaved caspase 3, but increased the expression of phospho-c-Jun and c-JUN. (**E**) IHC staining showed that the expression levels of BiP, P4HB, phospho-eIF2a, and phospho-c-JUN were increased in PTR mice compared to PS mice.

Aim 3: (**a**) *Examining dose response of CARB using PSTR cells*. Male nude mice (Jackson Lab) bearing subQ implanted tumors were treated with different doses of CARB (30, 50, and 80 mg/kg). Tumors sizes were monitored by weekly measurement (**Figure 5**). We chose 30 mg/kg was chosen for the combination study since it consistently reduced tumor growth by ~20% at the endpoint.

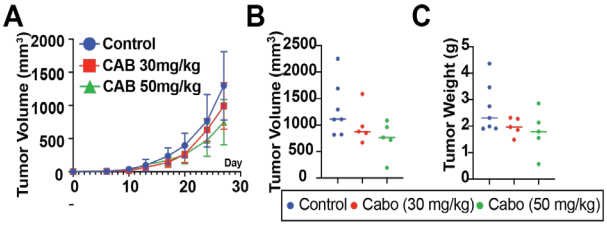

Figure 5. The effect of carboplatin on the growth of subQ 144-13 tumors as shown weekly measurement of tumor volume (**A**) and tumor volume (**B**)/weight (**C**) at the endpoint.

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

Nothing to Report.

How were the results disseminated to communities of interest?

Nothing to Report.

What do you plan to do during the next reporting period to accomplish the goals?
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. Determine the role of KDM4A in NEPC progression using organoids, PDXs, and GEMMs. We will examine the effect of KDM4A knockdown and inhibition using QC6352 on the proliferation and apoptosis of organoids derived from MDA PCa 144-13 and MDA PCa 155- PDXs. We will examine the effect of Kdm4a KO on tumor progression and survival using in genetically engineered mouse models (GEMMs).
Aim 2. Examine the mechanism(s) by which KDM4A regulates UPR signaling. We will delineate the mechanisms by which KDM4A regulates NEPC progression through integrative ChIP-seq and RNA-seq analyses, with a focus on the regulation of unfolded protein response by KDM4A. We will also acquire human prostate tumor samples and perform IHC staining of important regulators of UPR.
Aim 3. Determine whether KDM4 inhibitors improve the therapeutic outcomes of platinum-taxane chemotherapy in NEPC. We will examine whether QC6352 enhance the response of NEPC to cabazitaxel (CBTX) and carboplatin (CARB) in GEMMs and PDXs.

4. IMPACT

D*escribe 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?

Nothing to Report.

What was the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

Nothing to Report.

5. CHANGES/PROBLEMS

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 NEPC progression through regulation of MYC expression. Cancer Research [under review, also deposited into bioRxiv, 2022.2005.2014.491739 (2022). https://doi.org:10.1101/2022.05.14.491739]

  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: "Transcriptional and epigenetic dysregulations in prostate cancer progression", Research Seminar Series at UT Health McGovern Medical School, Institute of Molecular Medicine 2021-2022 The Brown Foundation Institute of Molecular Medicine, TX, 11/2021

- **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. Describe the technologies or techniques were 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. 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 database**s: (1) a RNA-seq data generated from Kdm4a KD PTR cells and control PTR cells; (2) a ChIP-seq dataset from 144-13 cells using antibodies for KDM4A, H3K9me3, H3K27ac, H3K36me3, and CTCF.
  - **Research material**: (1) mouse NEPC cell lines PTR and PSTR, (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".*

Name:	**Guocan Wang**
Project Role:	Principal Investigator
Research Identifier (e.g. ORCID ID):	0000-0002-8922-7249
Nearest Person Months Worked:	2 calendar months
Contribution to Project:	Dr. Wang is responsible for the overall oversight and direction of this proposal.
Funding Support:	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

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 (3/2022-8/31/2022)
Research Identifier (e.g. ORCID ID):	N/A
Nearest Person Months Worked:	12 calendar months
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)

Prostate Moon Shot	*(Logothetis/Aparicio/Navin)*
Title:	*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, 713-792-3477, Research_Finance@mdanderson.org
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

(NEW)

CGC-FY22-02	*(Wang)*
Title:	*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, PhD; 713-500-3631, cgc@uth.tmc.edu
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

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. Feighl, 713-792-3477, Research_Finance@mdanderson.org
Performance Period:	12/17/2021-12/16/2023
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

(THIS AWARD)

Grant No (PI):	*W81XWH-21-1-0522 (Wang)*
Title:	*PC200420: Targeting Histone Lysine Demethylase KDM4A in Neuroendocrine Prostate Cancer*
Effort:	1.80 calendar months (15% effort)
Supporting Agency:	DOD-PCRP Idea

Grants Officer: Kimberly Carter, 301-619-2249, Kimberly.m.carter47.civ@mail.mil
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

RP220410 *(Rai)*
Title: *Mechanisms and Therapies Focused on Epigenomic Alterations in Therapy-Resistant Prostate Cancers*
Effort: 1.20 calendar months (10% effort)
Supporting Agency: CPRIT
Grants Officer: Patty Moore, 512-463-3190, pmoore@cprit.texas.gov
Performance Period: 03/01/2022-02/28/2025
Level of Funding:
Project Goals: 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.
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

PREVIOUS (Recently completed)
P50 CA140388-10 *(Logothetis/Thompson)*
Title: *Developmental Research Program award: Investigate Co-Inhibition of Histone Lysine Demethylase KDM4 and PARP1 as a Novel Synthetic Lethal Approach in Prostate Cancer*
Effort: 1.20 calendar months (10% effort)
Supporting Agency: NIH/NCI – Developmental Research Program (DRP)
Grants Officer: Ashley Salo, ashley.salo@nih.gov
Performance Period: 09/01/2020-08/31/2022 NCE
Level of Funding:
Project Goals: Our overall goal is to identify a broadly effective PARPi-based combination therapy strategy for prostate cancer patients without DDRm and predictive biomarkers for the therapeutic response for quick bench to bedside translation.
Specific Aims: 1. Determine the efficacy of KDM4i combined with PARPi.
2. Elucidate the mechanisms underlying the efficacy of KDM4i in combination with PARPi.

3. Identify biomarkers in prostate cancer exosomes for predicting the therapeutic response to KDM4i mono- and combination therapy.
4. Characterize the association of KDM4A expression with ER stress in human prostate cancer samples.

Role: Principal Investigator, DRP award
Overlap: None

APARICIO

CURRENT

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, ashley.salo@nih.gov
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: Co-Investigator, Project 1
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% effort)
Supporting Agency: Janssen Pharmaceuticals Inc.
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

W81XWH-20-10257 *(Aparicio)*
Title: *PC190353: Chemoimmunotherapy for Aggressive Variant Prostate Cancers (AVPC)*
Time Commitments: 1.20 calendar months (10% effort)
Supporting Agency: DOD
Grants Officer: Kenneth E. Grenier, kenneth.e.grenier2.civ@mail.mil
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

(THIS AWARD)
W81XWH-21-1-0522 *(Wang)*
Title: *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, Kimberly.m.carter47.civ@mail.mil
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

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 calendar months
Supporting Agency: Amgen Inc.
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

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).
Aims: Primary objectives: 1. Determine the maximum tolerated dose (MTD) and confirm the safety and tolerability of valemetostat (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 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

<u>PREVIOUS</u> (Recently completed)

Prostate Moon Shot *(Logothetis)*
Title: *Prostate Cancer Moon Shot*
Project 2: An Integrated Definition and Therapeutic Strategy for Androgen Indifferent Prostate Cancers
Time Commitment: 0 calendar months, unsalaried
Supporting Agency: MD Anderson Moon Shot Program
Grants Officer: Carrie C. Feighl, research_finance@mdanderson.org
Performance Period: 09/01/2021-08/31/2022
Level of Funding: annual direct
Goal(s): To develop effective therapies for the androgen indifferent prostate cancers, a subset with dismal prognosis and very limited treatment options.
Specific Aims: 1. Stratify the AVPC based on integrated genomic and tumor compartment-specific transcriptomic signatures across prospective clinical trials spanning the natural history of advanced prostate cancers.

2. Determine the effects of valemetostat and cabazitaxel-carboplatin on the epithelial and immune compartments of AVPC tumors.

Role: Project Lead
Overlap: None

LEE, Min Gyu

CURRENT

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, mimi.bui@nih.gov
Performance Period: 06/07/2017-05/31/2023 (NCE)
Level of Funding:
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

(NEW)
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

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, 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

(THIS AWARD)
W81XWH-21-1-0522 *(Wang)*
Title: *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, Kimberly.m.carter47.civ@mail.mil
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 *(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, Manda.richards@nih.gov
Performance Period: 07/01/2020-06/30/2025
Level of Funding:
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

(NEW)
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, nailah.shaw@nih.gov
Performance Period: 08/09/2022-07/31/2027
Level of Funding:

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)

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.21 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 Principal Investigator (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/eBRAP/public/index.htm*** *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.*

Not applicable