AWARD NUMBER: **W81XWH-15-1-0628**

TITLE: **Targeting Dysregulated Epigenetic Enzymes for Prostate Cancer Treatment**

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REPORT DATE: **October 2017**

TYPE OF REPORT: **Annual**

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

DISTRIBUTION STATEMENT: **Approved for Public Release;**
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
October 2017	Annual	30 Sep 2016 - 29 Sep 2017

4. TITLE AND SUBTITLE
Targeting Dysregulated Epigenetic Enzymes for Prostate Cancer Treatment

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-15-1-0628

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Wisconsin – Madison
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

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

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
This proposal provides an unbiased identification of aberrant enzymatic activities and histone PTM states in the development of castrate-resist PCa (CRPC). Using the peptide-microarray technology to obtain preliminary data, we found changes in hormone sensitive LNCaP and its castrate-resistant PCa clone CT-4 that identified several altered histone H3 acetyltransferases and deacetylases. We will apply this workflow t establish whether these enzymes are commonly dysregulated in other castrate-resistant PCa cell lines and in human PCa tissues, or whether distinct sets of epigenetic modifiers drive resistance in different patients. **Based on these data we hypothesize that specific histone-modifying enzymes altered during the development of castrate-resistant PCa (CRPC) can be targeted therapeutically.**
We propose 3 Specific Aims: *1*.) To identify dysregulated epigenetic enzymes in hormone-sensitive and CRPC, *2*.) To validate altered PTM states in human samples from hormone-sensitive and CRPC. *3*.) To provide proof-of–concept that CRPC is dependent on these aberrant enzyme activities and therefore responsive to small-molecules that target their activity. This novel study provides an unbiased identification of aberrant enzymatic activities and histone PTM states in CRPC. This understudied area in PCa is significant not only in identifying biomarkers for diagnosis and prognosis, but in providing a therapeutic strategy that targets epigenetic mechanisms.

15. SUBJECT TERMS
Peptide microarray, histone post-translational modification, epigenetics, prostate cancer, p300, lysine acetylation, deacetylation, Sirtuins, hormone-sensitive (HS), castrate-resistance (CR)

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	11	**19b. TELEPHONE NUMBER** *(include area code)*

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1. Introduction

Prostate cancer (PCa) progression involves genetic alterations, but also dynamic epigenetic mechanisms resulting in gene expression changes critical for tumorigenesis. One major epigenetic process is the post-translational modification (PTM) of histone proteins, which wrap DNA and controls its accessibility for specific gene expression. There is growing evidence that dysregulation of enzymes that add or remove these PTMs is at the nexus of cancer initiation and progression. Therefore, new therapeutics for treating PCa lie in the identification of these aberrant enzyme activities and elucidating their role in PCa progression. To identify dysregulated chromatin enzymes, we have recently developed two novel methodologies. One approach utilizes a peptide-array technology to assay enzymatic activities on ~1000 unique histone peptides that differ in their sequence and PTM state. The second complementary approach is our recently developed LC-MS/MS method that allows simultaneous quantification of 60 histone PTM states from endogenous tissues and cells. This proposal provides an unbiased identification of aberrant enzymatic activities and histone PTM states in the development of castrate-resistant PCa (CRPC). Using the peptide-microarray technology to obtain preliminary data, we found changes in hormone sensitive LNCaP and its castrate-resistant PCa clone CT-4 that identified several altered histone H3 acetyltransferases and deacetylases. We will apply this workflow to establish whether these enzymes are commonly dysregulated in other castrate-resistant PCa cell lines and in human PCa tissues, or whether distinct sets of epigenetic modifiers drive resistance in different patients. **Based on these data we hypothesize that specific histone-modifying enzymes altered during the development of castrate-resistant PCa (CRPC) can be targeted therapeutically.** We propose 3 Specific Aims: *1*.) To identify dysregulated epigenetic enzymes in hormone-sensitive and CRPC, *2*.) To validate altered PTM states in human samples from hormone-sensitive and CRPC. *3*.) To provide proof-of–concept that CRPC is dependent on these aberrant enzyme activities and therefore responsive to small-molecules that target their activity. This novel study provides an unbiased identification of aberrant enzymatic activities and histone PTM states in CRPC. This understudied area in PCa is significant not only in identifying biomarkers for diagnosis and prognosis, but in providing a therapeutic strategy that targets epigenetic mechanisms.

2. Keywords

3. Accomplishments

Accomplishments Major Task 1: Identify dysregulated histone acetyltransferase (HAT) and deacetylase (HDAC) activities in Castration-Resistance Prostate Cancer (CRPC) cells and xenografts during progression from androgen dependence (AD).

Subtask 1: Measurement of endogenous acetylation and deacetylation activities in LNCaP and C4-2 cell lines (plus two additional AD/CRPC sets) and 5 LuCAP xenograft AD/CRPC sets by using histone peptide microarray assay. Statistical analysis for significance of microarray and to identify lysine acetylation sites displaying high divergence between the two cell lines.
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Completed. We have performed this analysis in 3 cell lines and 12 xenografts. This information is included in the recently published Lee manuscript (Figure 1-2, Figure 5).

Subtask 2: Validation of the HAT activity from HTS histone peptide microarray analysis by time-course filter-binging HAT assays using synthetic histone peptides and radiolabeled 3H-AcCoA as substrates.

Completed. Lee manuscript (Figure 3).

Subtask 3: Validation of the sirtuin activity identified in the microarray result by in vitro biochemical method using a nicotinamide-dependent enzyme-coupled system.

Completed. Lee manuscript (Figure 4).

Subtask 4: Identification and validation of novel HAT and HDAC activities on specific targets

Completed for P300 and Sirt2 and data included in Lee manuscript (Figure 4 and 5). We have noted that the downregulation of Sirt2 in cell lines and human prostate cancer (CRPC) is a key driver of this change in P300 acetylation.

In another publication (Damadoran et al., BMC Cancer) we extended our analysis of alterations in this SIRT2 - histone H3K18 acetylation pathway by examining these in human samples. As these enzymes represent an important target for cancer therapy, we sought to determine whether the underlying genes are altered during prostate cancer (PCa) progression. Tissue microarrays generated from 71 radical prostatectomy patients were initially immunostained for H3K18Ac, P300 and SIRT2. Protein levels were quantified using VECTRA automation and correlated with clinicopathologic parameters. The Cancer Genome Atlas (TGCA, n = 499) and Gene Expression Omnibus (n = 504) databases were queried for expression, genomic and clinical data.

We found that nuclear histone H3K18Ac staining increases in primary cancer ($p = 0.05$) and further in metastases ($p < 0.01$) compared to benign on tissue arrays. P300 protein expression increases in cancer ($p = 0.04$) and metastases ($p < 0.001$). A progressive decrease in nuclear SIRT2 staining occurs comparing benign to cancer or metastases($p = 0.04$ and $p = 0.03$ respectively). Decreased SIRT2 correlates with higher grade cancer ($p = 0.02$). Time to Prostate Specific Antigen (PSA) recurrence is shorter in patients exhibiting high compared to low H3K18Ac expression (350 vs. 1542 days respectively, $P = 0.03$).

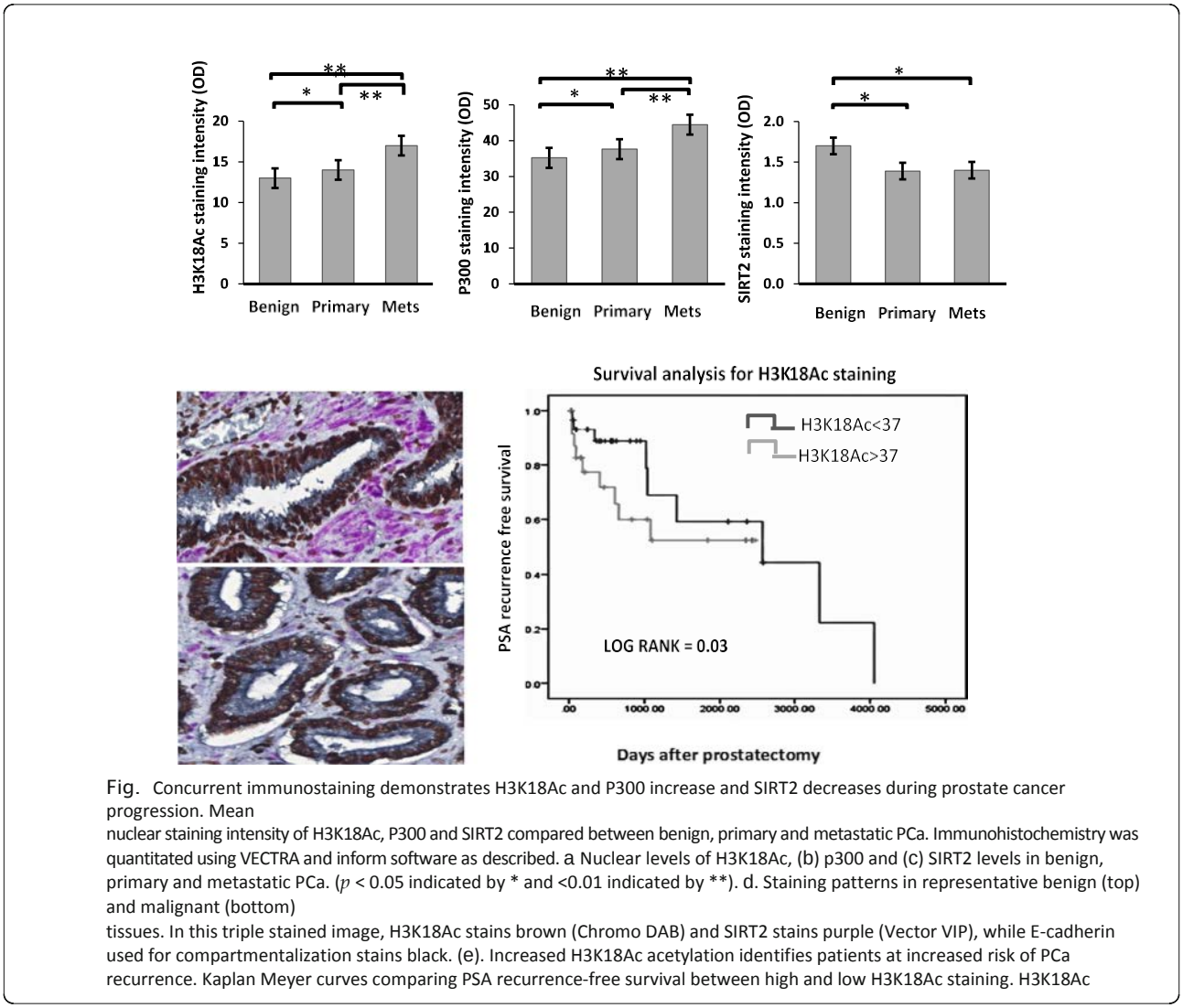


Fig. Concurrent immunostaining demonstrates H3K18Ac and P300 increase and SIRT2 decreases during prostate cancer progression. Mean
nuclear staining intensity of H3K18Ac, P300 and SIRT2 compared between benign, primary and metastatic PCa. Immunohistochemistry was quantitated using VECTRA and inform software as described. a Nuclear levels of H3K18Ac, (b) p300 and (c) SIRT2 levels in benign, primary and metastatic PCa. ($p < 0.05$ indicated by * and <0.01 indicated by **). d. Staining patterns in representative benign (top) and malignant (bottom)
tissues. In this triple stained image, H3K18Ac stains brown (Chromo DAB) and SIRT2 stains purple (Vector VIP), while E-cadherin used for compartmentalization stains black. (e). Increased H3K18Ac acetylation identifies patients at increased risk of PCa recurrence. Kaplan Meyer curves comparing PSA recurrence-free survival between high and low H3K18Ac staining. H3K18Ac

In GEO, SIRT2 mRNA levels are lower in primary and metastatic tumors ($p = 0.01$ and 0.001, respectively). TGCA analysis demonstrates SIRT2 deletion in 6% and increasing clinical stage, positive margins and lower

PSA recurrence-free survival in patients with SIRT2 loss/deletion (p = 0.01, 0.04 and 0.04 respectively). In this dataset, a correlation between decreasing SIRT2 and increasing P300 mRNA expression occurs in tumor samples (R = −0.46).

We conclude that in multiple datasets, decreases in SIRT2 expression portend worse clinicopathologic outcomes. Alterations in SIRT2-H3K18Ac suggest altered P300 activity and identify a subset of tumors that could benefit from histone deacetylation inhibition.

Milestone(s) Achieved:
-Identification and validation of novel HAT and HDAC activities on specific targets including P300 and Sir2. Others identified and included in the attached submitted manuscript.

We developed a high-throughput peptide microarray assay to identify altered histone lysine (de)acetylation activity in prostate cancer (PCa). This microarray-based activity assay revealed up-regulated histone acetyltransferase (HAT) activity against specific histone H3 sites in a castrate-resistant (CR) PCa cell line compared to its hormone-sensitive (HS) isogenic counterpart.

NAD^+-dependent deacetylation assays revealed down-regulated Sirtuin activity in validated CR lines. Levels of acetyltransferases GCN5, PCAF, CBP and p300 were unchanged between matched HS and CR cell lines. However, auto-acetylation of p300 at K1499, a modification known to enhance HAT activity and a target of deacetylation by SIRT2, was highly elevated in CR cells.

Among all 7 Sirtuins, only SIRT2 and SIRT3 protein levels were reduced in CR cell lines.

Interrogation of HS and matched CR xenograft lines reveals that H3K18 hyperacetylation, increased p300 activity, and decreased SIRT2 expression are associated with progression to CR in 8/12 (66%).

Tissue microarray analysis revealed that hyperacetylation of H3K18 is a feature of CRPC. This is associated with loss of SIRT2 expression (Figure 5). Inhibition of p300 results in lower H3K18ac levels and increased expression of androgen receptor.

In primary cancer sets H3K18 acetylation and SIRT2 loss associate with worse clinical outcomes. SIRT2 may be a biomarker for patients who could be treated with acetylation inhibitors. (Damadoran et al 2017)

Thus, a novel histone array identifies altered enzyme activities during the progression to CRPC and may be utilized in a personalized medicine approach.

Reduced SIRT2 expression and increased p300 activity lead to a concerted mechanism of hyperacetylation at specific histone lysine sites (H3K9, H3K14, and H3K18).

Major Task 2: Demonstrate corresponding PTM state dysregulated in CRPC cells, xenografts, and human tissues compared to AD state.

Subtask 1: Sample preparations for endogenous histone extraction from the AD and CRPC sets including LNCaP and C4-2

We have performed LC-MS/MS data for 12 paired AD and CRPC xenograft tumor sets (from University Washington/ DOD repository). The LuCaP PDX series is comprised of human PC samples subcutaneously implanted and propagated in immunodeficient mice. Tumors were obtained from AD and CRPC matched samples.

Subtask 2: Acquisition of LC-MS/MS data of samples prepared in 2.1. Quantitative analysis of specific histone modifications using Q-Exactive. Generate stable cell lines expressing plasmids developed in task 3.1

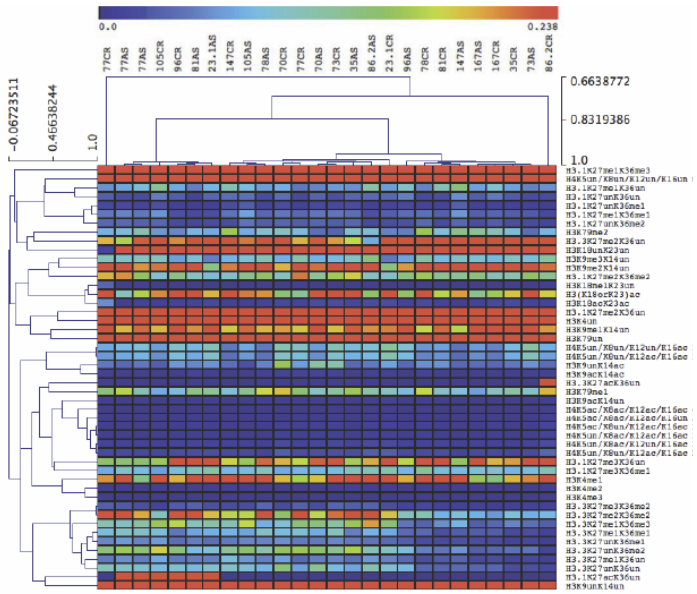
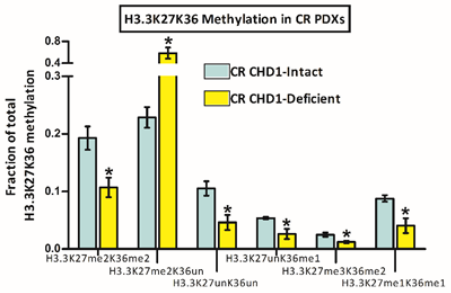


Figure 1: Hierarchical clustering heatmap of histone modification abundance in LuCaP PDX samples as determined by LC-MS/MS. The individual PDX samples are listed across the top of the figure with respect to hierarchical clustering. AS = androgen sensitive, CR = castration resistant. Histone peptides are shown along the right hand side of the heat map with respect to clustering. Colors indicate relative abundance of each modified histone peptide, scale shown on top ranges from 0.0 to 0.238. Dendrograms along top and left side represent clustering of PDX samples and histone peptides, respectively, with distance indicated.

Quantitative analysis of LC-MS/MS data has been performed. This demonstrates alterations in multiple histone modifications. A heatmap for these alterations has been performed and is shown in the figure.
This analysis defines specific histone marks. This redemonstrated changes in H3K18, H3K14 and H3K9. This analysis allows the assessment of specific histone modifications and combinations of modifications. A summary of the histone changes are provided in Figure 2A. We note a range of changes in CRPC PDX samples compared to their androgen sensitive counterparts. This is highlighted in Figure 2B demonstrating H3K9UnK14Ac across all xenografts. Note that some have marked increases in this mark, while others have a decreases (#167, 86). This was not unexpected given variation in the genetic background of human tumors.

We examined further this data by comparing the known genetic background of these samples and correlating it with the epigenetic results. Our initial LC-MS/MS analysis demonstrated a remarkable finding, that levels of histone PTM states, primarily H3.3K27K36 methylation, were significantly decreased in *CHD1*-deficient compared to *CHD1-intact* CR PDX samples. The *CHD1*-deficient CR PDX samples showed significant reductions in higher-order (me2, me3) H3.3K27K36 methylation with a significant increase in H3.3K27me2K36un states when compared to *CHD1*-intact CR PDX samples (Figure 2, top). *These results suggests that PTM of H3K27K36 are regulated by the genetic status of CHD1 in CRPC, a remarkable observation. CHD1* is a DNA-binding protein known to regulate chromatin assembly and transcription. *CHD1* is deleted in 11% of prostate cancer TCGA tumors and is one of the most commonly altered genes in prostate cancer.

Further analysis of the enzymes underlying this alteration in H3K27K36 are in process. We will examine by expression a panel of genes known to alter this and further interrogate this pathway with inhibitors.



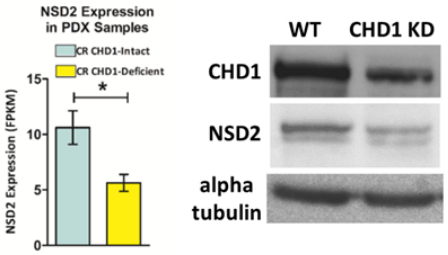


Figure 2. Reduced levels of H3.3K27K36 methylation in *CHD1*-deficient CR PDX samples. Top: fractional abundance of indicated H3.3K27K36 PTM peptides in CR PDX samples. Note shift towards H3.3K27me2K36un, and decrease in other peptides, specifically H3.3K27me2K36me2. Sum of all H3.3K27K36 peptide states = 1.0, Student's t-test (p*0.05) Bottom right: Immunoblot showing *CHD1* and NSD2 levels in *CHD1*-KD LNCaP cells. Bottom Left: NSD2 expression in CR PDX samples, Student's t-test (p*0.05)

Subtask 3: Western blot analysis of endogenous histone extraction from LNCaP and C4-2 cells/xenogafts/human tissues by probing with histone PTM-specific antibodies (sp. H3K9ac, H3K14ac, H3K18ac, and H4K20ac) that are relevant to CRPC and the result obtained in Task 1.

Performed. As noted above we have performed this with H3K9, H3K14 and H3K18 (published in Lee et al).

Milestone(s) Achieved: Demonstrated PTM states dysregulated in AD and CRPC cells/xenografts. Changes in H3K18, H3K14 and H3K9 acetylation. Other changes as detailed.
Striking finding of genetic background defining which patterns of histone modifications are seen. Further examination of the enzymes underlying these changes ongoing.

Major Task 3: Identify histone modifying proteins (e.g. HATs and Sirtuins) that drive CRPC.

Subtask 1: Test for p300 inhibition using C646, in C4-2 cells and one or more transfectable CRPC cell line. Probe changes in acetylation.

Performed C646 inhibition and results reported in attached manuscript (Lee et al, Figure 5).

Subtask 2: Preparation of siRNA knockdown of p300 in C4-2 cell line and at least one other cell line. Evaluation of efficiency for siRNA knockdown by gene expression and western blotting.

Ongoing.

Subtask 3: Overexpression of Sirt6 in C4-2 cell lines using Sirt6-expression construct (previously prepared in the Denu lab). Analysis of Sirt6 expression.

Ongoing. Sirt6 expression was not downregulated in the C4-2 cell line with repeated studies. In contrast Sirt2, 3 and 4 were. Attached manuscript Figure 4.

Subtask 4: Time-course experiment for comparison of phenotypic behaviors (e.g. cell growth, apoptosis, senescence, acetylation levels on target genes, and gene transcript abundance) in 6 different samples; (1) WT LNCaP cells, (2) WT C4-2 cells, (3) C4-2 with p300 inhibition, (4) C4-2 with Sirt6 FA-activation, (5) C4-2 with p300 knockdown, and (6) C4-2 with Sirt6 overexpression.

Ongoing. Cell growth apoptosis and transcript alterations has been performed for P300 downregulation with C646 (Figure 5) in several cell lines

Subtask 5: Evaluation of additional statistically altered modifying enzymes identified in Task 1-2, using the similar workflow as described in 3.1-3.4. Assess if available small molecular inhibitors/preclinical agents against these enzymes.

Given our findings regarding the role of P300 Acetylation we performed inhibition studies and published this in our recent manuscript (Lee et al., 2017).

Further work regarding the altered histone methyltransferase patterns is ongoing with targeted inhibition of these will be performed in the final year of the grant.

Milestone(s) Achieved:

Confirmed that CRPC is dependent on these activities and tested inhibitors as therapeutic approach using the agent C646. Further small molecule and novel drug studies planned for additional altered enzymes underlying histone methyltransferase.

Opportunities for training and professional development?

These include post-doctoral student Dr Jin-Hee Lee who was the primary author of the completed study and has completed her training. She has taken a research position with a company focused on therapy development (Covance Inc, Madison WI). Replacing her is Joseph Gawdzik PhD who is a recent graduate in Pharmacology and has been continuing the work on Task 2 and 3.

How were the results disseminated to communities of interest?

Published 2 papers. Abstract presentation at the Prostate Cancer Foundation meeting 10/2016. Presented abstract at the AUA meeting in 4/2017.

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

An additional paper is planned looking at results from the LC-MS/MS. This will focus on altered histone methylation patterns and the enzymes underlying these changes. The models and analyses are set up to validate. We will additionally pursue the observation that the genetic background can

4. Impact

Emerging evidence indicates that targeting epigenetic mechanisms might provide a new paradigm for drug treatment in cancer. Increased HDAC activity in prostate tumors provides one target, and treatment with HDAC inhibitors (HDACi) such as Suberoylanilide Hydroxamic Acid (SAHA) and Phenylbutyrate (PB) induce pro-apoptotic and growth inhibitory effects. In Phase I studies in advanced solid tumors including prostate biomarker evaluations have demonstrated an accumulation of acetylated histones and H4 indicating a target effect. A major hurdle with these approaches is a lack of selective targeting of modifications, a primary goal of the current proposal.

We have used two new high-throughput assay platforms to identify different epigenetic states during the transformation from hormone-sensitive to CRPC. The CHIP assay we developed we are attempting to downsize in order to directly assess tumor biopsy tissue for histone modifications. CRPC provides the initial target for this newer class of therapy given the focus of the PCRP on developing new effective treatments for men with high risk prostate cancer.
Our data suggests that men with decreased SIRT2 expression have high P300 acetylation levels and would benefit patients with CRPC. Development of small molecule A-485 (Lasko 2017) is currently in trials and this would offer a biomarker for potential responders.

Obtaining further histone modification information will permit us to be able to identify specific enzymes that are altered during PCa progression and examine *in vitro* and *in vivo* the effect of specific inhibitors of these enzymes on CRPC growth and viability. This will provide a rationale for the application of inhibitors, many that have been synthesized but not developed further, to patients overexpressing these enzymes in a personalized medicine approach. Finally, the identification of specific post-translational modifications associated with the development of CRPC may mark tumors at risk for progression to lethal disease permitting earlier intervention in these patients.

5. Changes Problems

Nothing to report.

6. Products

Journal publications

1. Lee JH, Yang B, Lindahl AJ, Damaschke N, Boersma MD, Huang W, Corey E, **Jarrard DF**, Denu JM. Identifying Dysregulated Epigenetic Enzyme Activity in Castrate-Resistant Prostate Cancer Development. ACS Chem Biol. 2017 Nov 17;12(11):2804-2814. PubMed PMID: 28949514
2. Damodaran S, Damaschke N, Gawdzik J, Yang B, Shi C, Allen GO, Huang W, Denu J, **Jarrard D**. Dysregulation of Sirtuin 2 (SIRT2) and histone H3K18 acetylation pathways associates with adverse prostate cancer outcomes. BMC Cancer. 2017 Dec 20;17(1):874. PubMed PMID: 29262808; PubMed Central PMCID: PMC5738829.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Senior key personnel have been working on the project since the initiation of the project with no changes.

The following individuals have worked on the project:

Name: David F. Jarrard, MD
Project Role: Principal Investigator
Researcher Identifier (e.g., ORCID ID):
Nearest person month worked: 3
Contribution to Project: David Jarrard has conceived and designed the study, reviewed all of the data and the analysis of all of the results on the project, wrote and revised the manuscript.

Name: John M. Denu, PhD
Project Role: Co-Principal Investigator
Researcher Identifier (e.g., ORCID ID):
Nearest person month worked: 3
Contribution to Project: John Denu has conceived and designed the study, reviewed all of the data and the analysis of all of the results on the project, wrote and revised the manuscript.

Name: Jin-Hee Lee, PhD
Project Role: Post-Doctoral Fellow
Researcher Identifier (e.g., ORCID ID):
Nearest person month worked: 0
Contribution to Project: Jin Lee has optimized the microarray-based enzyme assay platform, performed and analyzed the biochemical studies and immunoblot experiments, wrote and revised the Lee manuscript. She has taken a position with a biotechnology firm and been replaced by Dr Joe Gawdzik

Name: Joseph Gawdzik PhD
Researcher Identifier (e.g., ORCID ID):
Nearest person month worked: 3
Contribution to Project: Dr Gawdzik has analyzed the LC-MS/MS data of samples prepared in 2 and is performing the biochemical studies and immunoblot experiments for Tasks 2 and 3.

Name: Bing Yang, MD & PhD
Project Role: Researcher
Researcher Identifier (e.g., ORCID ID):
Nearest person month worked: 3
Contribution to Project: Bing Yang has prepared all the PCa cell lines used in this study and performed the transcriptomic analysis on the cell lines and the mouse xenografts.

Name: Eric A Armstrong, MS

Project Role: Associate Researcher
Researcher Identifier (e.g., ORCID ID):
Nearest person month worked: 1
Contribution to Project: Eric Armstrong has performed the LC-MS/MS runs.

Name: Nathan A. Damaschke
Project Role: Research Assistant
Researcher Identifier (e.g., ORCID ID):
Nearest person month worked: 0
Contribution to Project: Nathan Damaschke has analyzed human PCa cell line expression profile from GEO database repository and analyzed tissue microarray immunohistochemistry data. He has left to pursue a postdoctoral position at Northwestern University.

8. APPENDICES:

Lee JH, Yang B, Lindahl AJ, Damaschke N, Boersma MD, Huang W, Corey E, **Jarrard DF**, Denu JM. Identifying Dysregulated Epigenetic Enzyme Activity in Castrate-Resistant Prostate Cancer Development. ACS Chem Biol. 2017 Nov 17;12(11):2804-2814. PubMed PMID: 28949514

Damodaran S, Damaschke N, Gawdzik J, Yang B, Shi C, Allen GO, Huang W, Denu J, **Jarrard DF**. Dysregulation of Sirtuin 2 (SIRT2) and histone H3K18 acetylation pathways associates with adverse prostate cancer outcomes. BMC Cancer. 2017 Dec 20;17(1):874. PubMed PMID: 29262808; PubMed Central PMCID: PMC5738829.