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Award Number: W81XWH-18-1-0195

TITLE: Abiraterone Steroidal Metabolites as Biomarkers for Treatment Resistance in Prostate Cancer

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REPORT DATE: August 2019

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**
August 2019	Annual	1 Aug 2018 - 31 Jul 2019 9

4. TITLE AND SUBTITLE

Abiraterone Steroidal Metabolites as Biomarkers for Treatment Resistance in Prostate Cancer

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-18-1-0195

5c. PROGRAM ELEMENT NUMBER

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

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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

First-line treatment for advanced (metastatic) prostate cancer (PCa) is androgen deprivation therapy (ADT), either by surgical or medical castration. In many cases the cancer becomes resistant, and castration resistant prostate cancer (CRPC) develops. Abiraterone, given orally as the prodrug abiraterone acetate, is used to treat CRPC. Abiraterone treatment improves overall survival; however, drug resistance eventually occurs, and patients die. In our previous studies, we found that abiraterone is metabolized in patients to 7 steroidal metabolites. In vitro and in vivo studies showed that abiraterone metabolites had opposing activities toward prostate tumor cells. Overall this project aims to investigate the steroidogenic metabolism of abiraterone and identify biomarkers of resistance. Here, we studied the pharmacokinetics of abiraterone metabolites after a single dose of abiraterone acetate in healthy subjects and will use the data to normalize the levels of the metabolites in patients. I also found that in prostate cancer cell lines, abiraterone metabolites will shift the metabolism of endogenous steroids and also mediate the expression of the androgen receptor-regulated genes. In the following funding year I will confirm the results in other prostate cancer cell line and will evaluate the 7 metabolites in patients and determine the relationship between metabolite levels and patient clinical outcomes to identify a biomarker of treatment resistance.

15. SUBJECT TERMS
Abiraterone, Biomarkers, Castration sensitive prostate cancer

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

Prostate cancer (PCa) is a major health problem in the United States, being the most frequently diagnosed cancer and the second leading cause of cancer-related death in men. Abiraterone, giving as the pro drug abiraterone acetate, is a potent steroidal inhibitor of CYP17A1 which is approved to treat PCa patients. We have reported that in humans, abiraterone is metabolized by steroidogenic enzymes to at least 7 steroidal compounds. Further, *in vitro* and *in vivo* these abiraterone metabolites exert opposing effects with respect to prostate cancer progression. These findings suggest that abiraterone metabolism generates compounds that prevent CRPC progression and others that can cause treatment resistance in CRPC. Therefore, I hypothesize that abiraterone steroidal metabolites play a crucial role in the development of treatment resistance in CRPC and can serve as biomarkers that will predict resistance to abiraterone treatment in patients with metastatic castration-sensitive prostate cancer. In this project I will identify and confirm the identified abiraterone metabolites in patients with metastatic castration-sensitive PCa and determine the relationship between the metabolite levels and clinical outcomes, and then determine mechanistically whether the abiraterone metabolites are a direct or indirect cause of abiraterone resistance.

2. KEYWORDS:

Abiraterone, Biomarkers, Castration sensitive prostate cancer, *HSD3B1*

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Training-Specific Tasks:

Major Task 1: Training and educational development in prostate cancer research

Milestone(s) Achieved: Completion of Research Conduct and Human Subjects Training. (24 Months)

Presentation of project data at national meetings. (24 Months)

Research-Specific Tasks:

Specific Aim 1: Identify and confirm the identified abiraterone metabolites in patients with metastatic castration-sensitive PCa and determine the relationship between the metabolite levels and clinical outcomes.

Major Task 1: Generate a data set from an available pharmacokinetic study of abiraterone acetate.

Milestone(s) Achieved: Generating the reference value for each of the 7 steroidal metabolites to be used to compare with the metabolites values in the patients. (3 Months)

Major Task 2: Normalize the metabolite levels in patients.

Milestone(s) Achieved: generating the normalized value that will be correlate with the clinical outcomes. (12 Months)

Major Task 3: Correlate the metabolite levels with clinical outcomes.

Milestone(s) Achieved: Determination of correlation between the metabolites and the clinical outcome of each patient to define biomarkers for drug resistance. (12 Months)

Specific Aim 2. Determine mechanistically whether the abiraterone metabolites are a direct or indirect cause of abiraterone resistance.

Major Task 4: Determine the effect of abiraterone metabolites on steroidogenic enzymes *in vitro.*

*Milestone(s) Achieved: Determination of the effect of the metabolites on steroidogenic enzyme activity. (*20 Months)

Major Task 5: Determine whether abiraterone metabolites mediate AR-regulated gene expression *in vitro.*

*Milestone(s) Achieved: Determination of the effect of the metabolites on AR regulated gene expression; publication in peer review journals. (*24 Months)

What was accomplished under these goals?

Specific Aim 1: Identify and confirm the identified abiraterone metabolites in patients with metastatic castration-sensitive PCa and determine the relationship between the metabolite levels and clinical outcomes.

Major Task 1: Generate a data set from an available pharmacokinetic study of abiraterone acetate.

Milestone(s) Achieved: Generating the reference value for each of the 7 steroidal metabolites to be used to compare with the metabolites values in the patients. (3 Months)

Results: To correct for variations between the last AA dose and blood draw among individual patients with PCa, the abiraterone metabolite concentrations (D4A, 3-keto-5α-Abi, 3α-OH-5α-Abi, 3β-OH-5α-Abi, 3-keto-5β-Abi, 3α-OH-5β-Abi, and 3β-OH-5β-Abi) in the patients will be normalized to a pharmacokinetic PK study in healthy controls to account for their respective PK parameters. Samples from 15 healthy male volunteer were analyzed by LC-MS. In the PK study, the volunteers received a single dose of AA, 1000 mg, plasma samples were collected at -0.5 (pre-dose), 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 48, 72, and 96 hours, and analyzed for steroidal abiraterone metabolites by LC-MS/MS method. The results from this study were used to generate reference data for abiraterone and the metabolites. (**Table 1. and Figure 1**).

Major Task 2: Normalize the metabolite levels in patients.

Milestone(s) Achieved: generating the normalized value that will be correlate with the clinical outcomes. (12 Months)

Results: We received the Approval from the Human Research Protection Office (HRPO) to perform this study. However due to the fact that we were not able to recruit 80 patients for this study in the first year, we were not able to analyze the samples. We recruited 57 patients but only 36 started the treatment. This task will be postpone to the upcoming year.

Major Task 3: Correlate the metabolite levels with clinical outcomes.

Milestone(s) Achieved: Determination of correlation between the metabolites and the clinical outcome of each patient to define biomarkers for drug resistance. (12 Months)

Results: We planned to correlate the results with clinical outcomes as listed in sub task 1 of major task 3 we proposed to extract the genotype from these patients, we only had one patients with the mutated gene (**Table 2.**) so in this case we cannot compare the genotypes. This task will be postpone to the upcoming year.

Specific Aim 2. Determine mechanistically whether the abiraterone metabolites are a direct or indirect cause of abiraterone resistance.

Major Task 4: Determine the effect of abiraterone metabolites on steroidogenic enzymes *in vitro.*

*Milestone(s) Achieved: Determination of the effect of the metabolites on steroidogenic enzyme activity. (*20 Months)

Results: To study the effect of abiraterone metabolites on steroidogenic enzyme activity I used the prostate cancer cell line LnCaP. To $1*10^6$ cells, 1µM of the androgen with or without 1µM abiraterone metabolites were incubated for up to 72 hours. Samples were collected at 24, 48, and 72 hours. Media samples were then subject to LC-MS analysis to determine androgens as well as abiraterone metabolites. For this experiment the following androgens were tested: Dehydroepiandrosterone DHEA, 3β- Androsterone 3β-AST, and 3β-Androstanediol 3β-diol in the presence of the following abiraterone metabolites D4A, 3β-hydroxy-5α-Abi, and 3β-hydroxy-5β-Abi. Each sample was repeated three technical times and each experiment was repeated three times. As shown in **Figures 2-4**, abiraterone metabolites has an effect on androgen metabolism and can shift the pathways suggesting that abiraterone metabolites plays important role in regulating steroidogenesis. The results also suggest that DHEA is still detected and metabolized up to 72 hours, however 3β-AST and 3β-diol levels were low at 24 hours and 3β-diol cannot be detected at the 48 hour time point. This can be explained by the fact that both 3β-AST and 3β-diol can be radially glucoronidated via the UGT enzyme that is presence in LnCaP cells limiting our studies in these cell lines to the 24 and 48 hour time point for 3β-diol and 3β-AST respectively.

Major Task 5: Determine whether abiraterone metabolites mediate AR-regulated gene expression *in vitro.*

*Milestone(s) Achieved: Determination of the effect of the metabolites on AR regulated gene expression; publication in peer review journals. (*24 Months)

Results: I sought to test the effect of low concentration of 3-keto-5α-Abi “which we reported as an AR agonist” on AR regulated gene expression. for this purpose I used LAPC4 cells which are prostate cancer cell line that expresses the wild type AR. Cells were serum starved for 48 hours then were treated with following doses of 3-keto-5α-Abi: 10, 20, 50, 100, 200 nM for 48 hours. After RNA extraction and cDNA synthesis Quantitative PCR (qPCR) analysis was conducted in triplicate in an ABI 7500 Real-Time PCR machine (Applied Biosystems) using iTaq Fast SYBR Green Supermix with ROX (Bio-Rad) and primers for PSA and RPLP0. As shown in **Figure 5**, 3-keto-5α-Abi induces PSA expression at l00 and 200 nM levels but not at 10 or 50. I then sought to study the metabolism of 3-keto-5α-Abi in LAPC4 to better investigate the effect of this metabolite on PSA. Same conditions were repeated concurrently with three concentrations of 3-keto-5α-Abi 10, 50, and 200 nM to evaluate 3-keto-5α-Abi metabolism in LAPC4 and media samples were collected and were subject to LC-MS analysis to determine

3-keto-5α-Abi metabolism. I found that 3-keto-5α-Abi will be converted to 3α-OH-5α-Abi and 3β-OH-5α-Abi and that the percentage left of 3-keto-5α-Abi is almost 25 % regardless of the initial concentration (**Figure 6. & Table 3**). I then tested the 5α-Abi metabolites: 3-keto-5α-Abi, 3α-OH-5α-Abi, and 3β-OH-5α-Abi to see whether any of them has a direct effect on AR regulated gene expression and found that only 3-keto-5α-Abi will stimulate the gene expression (**Figure. 7**).

Table 1. Pharmacokinetic parameters of abiraterone and the seven steroidal metabolites.

Pharmacokinetic parameter	Summary statistics	Abiraterone	D4A	3-keto-5α-Abi	3α-OH-5α-Abi	3β-OH-5α-Abi	3-keto-5β-Abi	3α-OH-5β-Abi	3β-OH-5β-Abi
$AUC_{0-\infty}$ (ng·h/mL)	Min-Max	158.3 - 1720.6	2.66-22.24	9.26-237.1	2.46-97.95	1.41-32.19	2.65-70.52	25.78-208.73	30.6-521.90
	Mean	492.95	10.42	54.16	16.02	7.24	29.66	85.34	204.51
	SD	416.53	5.27	53.89	16.10	8.83	19.87	52.74	147.89
	%CV	84.50	50.54	99.50	100.54	122.06	66.99	61.80	72.32
AUC_{0-t} (ng·h/mL)	Min-Max	147.4-1699.5	2.33-15.88	7.91-226.1	1.35-61.1	0.46-29.40	1.40-54.37	15.75-160.38	30.16-448.94
	Mean	463.13	7.34	49.77	12.78	4.71	25.20	69.08	183.15
	SD	412.65	3.95	51.93	14.63	7.74	17.24	39.70	130.76
	%CV	89.10	53.75	104.34	114.46	164.33	68.40	57.47	71.39
C_{max} (ng/mL)	Min-Max	33.77-223.27	0.43-2.12	1.12-22.59	0.155-4.07	0.11-1.84	0.63-3.53	0.44-3.02	0.91-10.53
	Mean	90.09	0.91	5.54	1.09	0.42	1.51	1.41	4.55
	SD	59.00	0.47	5.17	0.98	0.44	0.72	0.71	2.91
	%CV	65.49	52.08	93.35	89.91	104.49	47.29	50.05	63.95
t_{max} (h)	Min-Max	1.0-4.0	1.0-4.0	1.5-4.0	4.0-8.0	2.0-6.0	1.5-12.0	2.0-72.0	6.0-48.0
	Mean	1.93	2.07	2.70	5.07	4.00	3.20	19.33	16.80
	SD	0.90	0.84	1.11	1.49	0.78	2.77	21.15	11.31
	%CV	46.74	40.76	41.29	29.34	19.61	86.55	109.39	67.31
$t_{½}$ (h)	Min-Max	6.20-30.00	2.13-54.23	6.74-46.04	1.98-35.44	2.24-74.53	3.45-46.44	13.54-45.71	11.05-31.00
	Mean	11.34	17.07	20.91	18.12	16.81	22.08	29.80	20.70
	SD	6.22	12.07	11.51	11.60	24.35	13.75	9.89	5.37
	%CV	54.87	70.70	55.05	63.98	144.87	62.25	33.20	25.93
t_{last} (h)	Min-Max	24.0-72.0	8.0-48.0	24.0-96.0	12.0-96.0	6.0-72.0	6.0-96.0	72.0-96.0	72.0-96.0
	Mean	35.20	25.33	62.40	39.20	21.71	69.20	92.80	94.40
	SD	17.84	10.44	26.91	25.03	23.97	28.94	8.44	6.20
	%CV	50.67	41.20	43.12	63.86	110.40	41.82	9.10	6.56
K_e (/h)	Min-Max	0.023-0.11	0.013-0.33	0.015-0.10	0.02-0.35	0.009-0.31	0.015-0.20	0.015-.051	0.022-0.063
	Mean	0.07	0.07	0.04	0.08	0.13	0.05	0.03	0.04
	SD	0.03	0.07	0.03	0.10	0.09	0.05	0.01	0.01
	%CV	35.81	111.66	56.65	119.06	72.74	92.88	37.71	29.57
MRT_{inf} (h)	Min-Max	5.99-19.72	4.55-62.27	8.20-59.76	6.28-49.26	5.97-105.52	6.73-67.54	27.58-83.14	25.74-70.77
	Mean	10.74	22.34	23.06	25.74	27.03	36.63	55.46	43.54
	SD	3.55	13.32	12.58	14.13	33.55	18.84	17.20	13.61
	%CV	33.07	59.63	54.56	54.88	124.13	51.43	31.01	31.26
V_z/F (L)	Min-Max	(1.07-10.5)E+04	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Mean	43536.12	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	SD	23576.37	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	%CV	54.15	N/A	N/A	N/A	N/A	N/A	N/A	N/A
CL/F (L/h)	Min-Max	581.2-6316.7	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Mean	3069.76	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	SD	1654.73	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	%CV	53.90	N/A	N/A	N/A	N/A	N/A	N/A	N/A

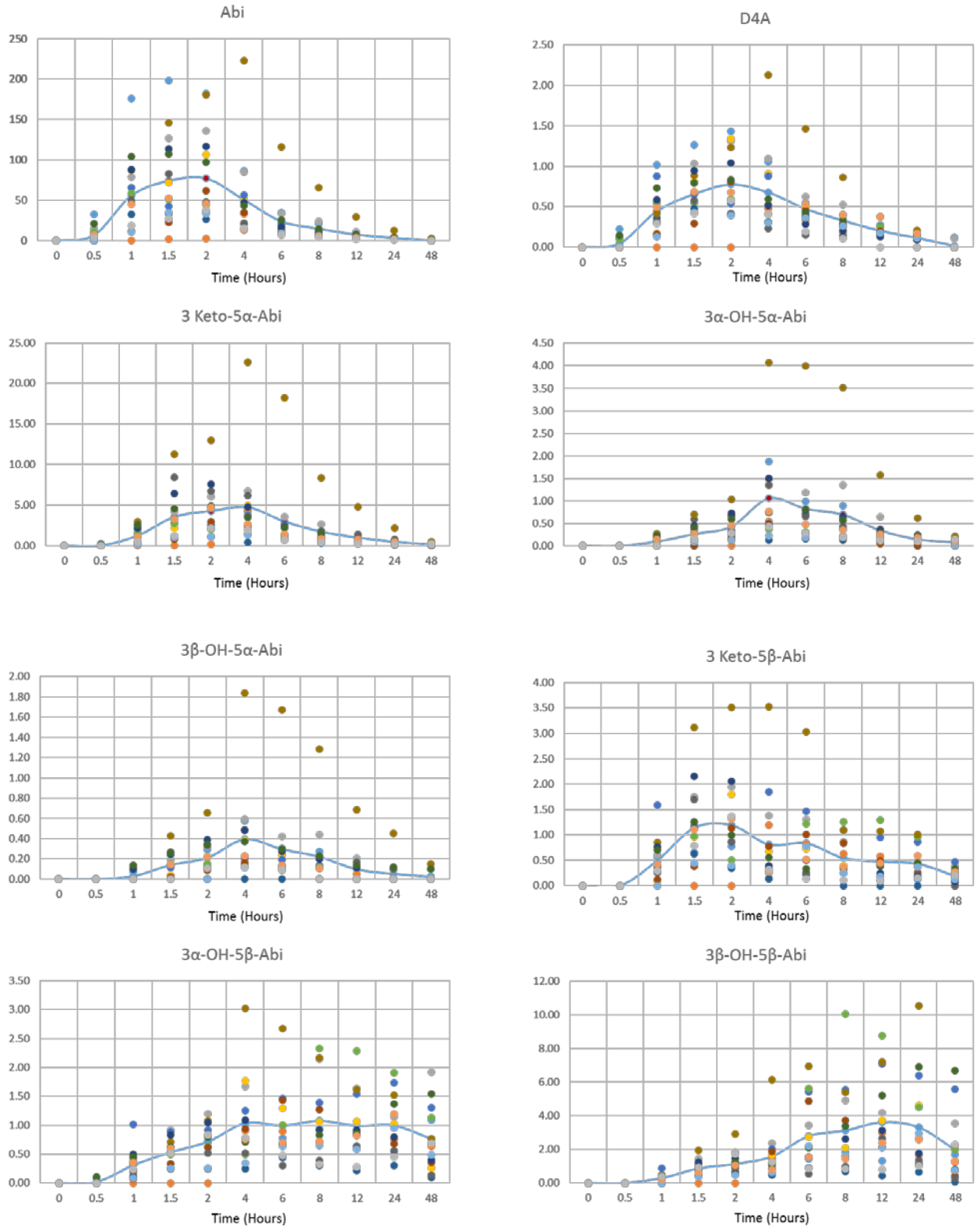
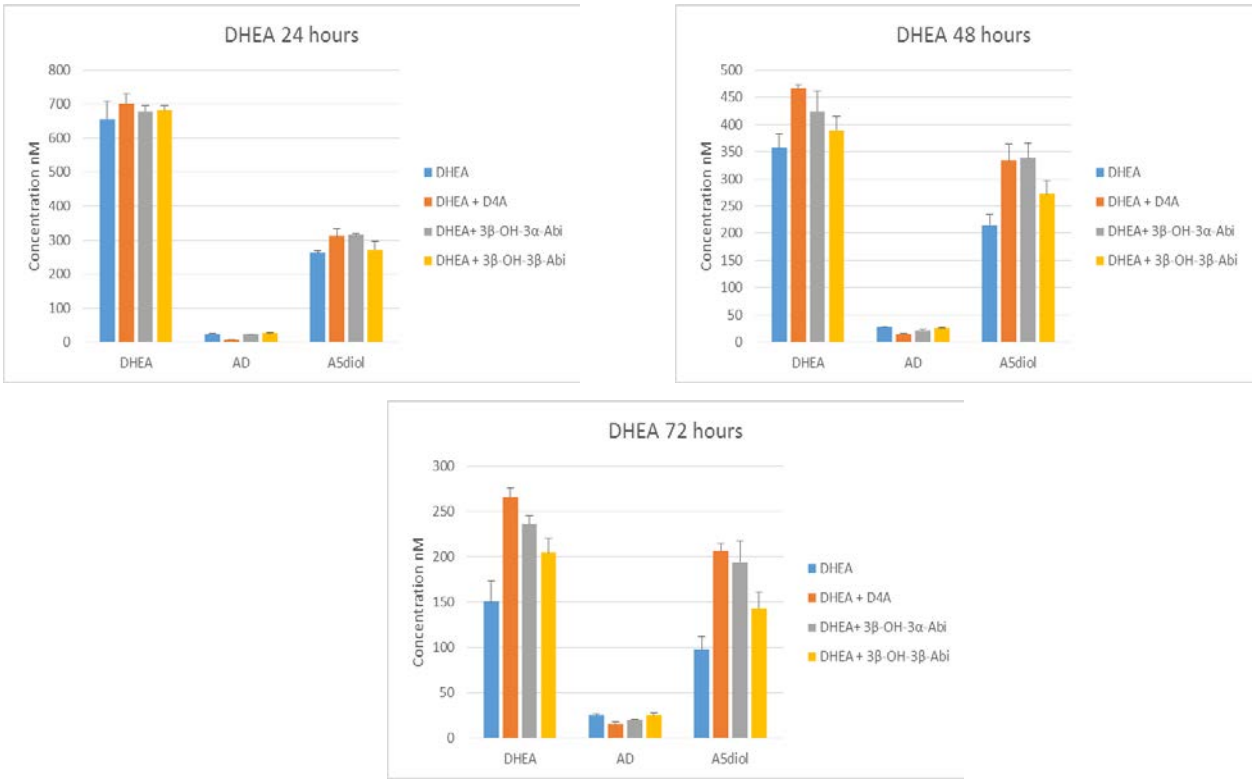


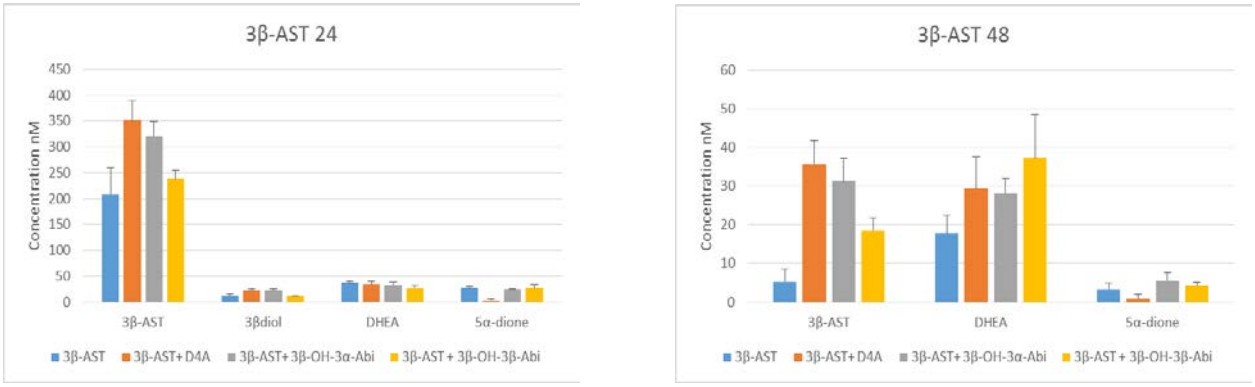
Figure 1. Mean plasma concentrations of abiraterone and steroidal metabolites after a single dose of AA in 15 healthy volunteers. The plasma concentration at each time point was used to generate the plots for A., Abiraterone, B., D4A, C., 3keto-5α-Abi, D. 3α-OH-5α-Abi, E. 3β-OH-5α-Abi, F., 3keto-5β-Abi, G. 3α-OH-5β-Abi, and H. 3β-OH-5β-Abi. The blue lines represent the mean concentration for each time point.

Table 2. Patients Characteristics.

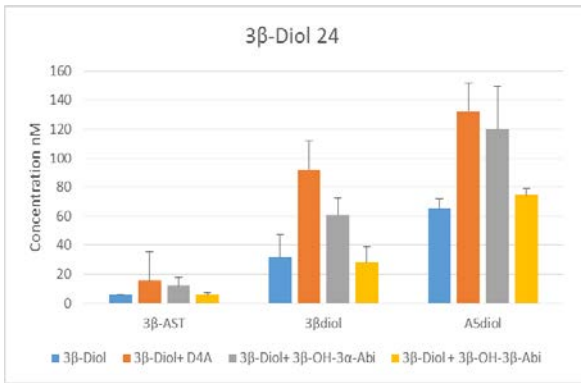
Sample ID	*HSD3B1* Genotype	Initial Baseline PSA	Age at Dx	Race	Pathology
1	MT	4.29	69	W	8
2	WT	3.91	62	W	7
3	WT	14.98	83	W	7
4	HZ	436.20	52	B	6
5	HZ	69.84	58	W	8
6	HZ	4.10	72	W	9
7	HZ	7.56	60	W	7
8	HZ	13.49	75	W	8
9	HZ	71.44	61	W	9
10	WT	52.35	70	W	9
11	HZ	19.00	73	W	9
12	HZ	160.70	52	B	10
13	WT	176.80	69	W	9
14	HZ	49.97	80	W	8
15	HZ	38.00	60	W	9
16	HZ	360.40	56	W	
17	WT	44.09	78	W	7
18	HZ	5.00	64	W	9
19	HZ	6.57	59	W	8
20	HZ	19.67	63	B	8
21	WT	3.50	58	W	7
22	WT	187.70	62	W	7
23	WT	11.90	58	B	9
24	HZ	42.67	79	W	8
25	WT	225.20	68	W	9
26	HZ	11.70	60	W	7
27	HZ	3.00	56	W	8
28	HZ	14.80	67	W	7
29	HZ	198.80	68	W	9
30	WT	104.50	63	W	10
31	WT	2.09	69	W	7
32	WT	6.28	72	W	7
33	WT	35.09	77	W	7
34	WT	4.90	55	B	
35	HZ	36.00	55	W	10
36	WT	103.00	56	W	9



Fgure 2. Representative plots of DHEA levels in LNCaP. 1 µM DHEA was incubated in LnCaP cells without or with1 µM D4A, 3β-hydroxy-5α-Abi, and 3β-hydroxy-5β-Abi for 24, 48 and 72 hours. Error bars represent three technical repeats.



Fgure 3. Representative plots of 3β-Androsterone (3β-AST) levels in LNCaP. 1 µM 3β-AST was incubated in LnCaP cells without or with1 µM D4A, 3β-hydroxy-5α-Abi, and 3β-hydroxy-5β-Abi for 24, 48 and 72 hours. Error bars represent three technical repeats.



Fgure 4. Representative plots of 3β- Androstanediol (3β-diol) levels in LNCaP. 1 µM 3β-diol was incubated in LnCaP cells without or with1 µM D4A, 3β-hydroxy-5α-Abi, and 3β-hydroxy-5β-Abi for 24, 48 and 72 hours. Error bars represent three technical repeats.

Figure 5. Effect of 3-keto-5α-Abi on AR target gene expression. 10^6 LAPC4 cells were treated with different doses of 3-keto-5α-Abi for 48 hours. Only 100 and 200 nM can stimulate PSA expression when normalized to control and RPLP0. Error bars represent SD of three technical repeats.

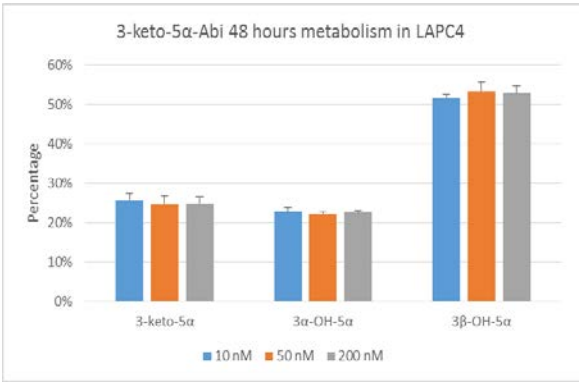


Figure 6. 3-keto-5α-Abi 48 hours metabolism. 10^6 LAPC4 cells were treated with 10, 50, and 200 nM of 3-keto-5α-Abi for 48 hours. Media samples were subject to LC-MS analysis. Error bars represent SD of three technical repeats.

Table 3. 3-keto-5α-Abi 48 hours metabolism in LAPC4

3-keto-5α-Abi treatment (nM)	3-keto-5α-Abi (nM)	3α-OH-5α-Abi (nM)	3β-OH-5α-Abi (nM)
10	1.13 (26%)	1 (23%)	2.27 (51%)
50	6.80 (25%)	6.13 (22%)	14.67 (53%)
200	28.33 (25%)	25.67 (23%)	60 (52%)

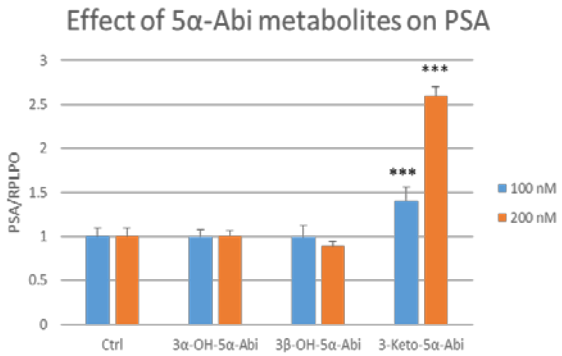


Figure 7. Effect of 5α-Abi metabolites on AR target gene expression. 10^6 LAPC4 cells were treated with 100 and 200 nM of different 5α-Abi metabolites for 48 hours. Only 3-keto-5α-Abi can stimulate PSA expression when normalized to control and RPLP0. Error bars represent SD of three technical repeats.

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

1. Attended Responsible Conduct of Research and Human Subjects Training.
2. Attended monthly Prostate Cancer Working Group and Seminar Series.
3. Attended and present research at the weekly lab meetings and journal clubs.
4. Attended and present my work at the weekly Cleveland Clinic Department of Cancer Biology seminars.
5. Attended and present at the bi-weekly Cleveland Clinic Department of Cancer Biology journal club.
6. Attended ENDO 2019
7. Attended workshop, Pharmacokinetics for Pharmaceutical Scientists Course in University of California San Francisco
8. Attended and completed Medical Biostatistics Part I and II courses at Cleveland Clinic.
9. Attended and completed Introduction to Clinical Research course at Cleveland Clinic.
10. Upcoming funding year: Attend workshop, Biomedical and Scientific Writing at the Kenyon Institute, Kenyon College, Gambier, OH.

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?
In the first year I was able to show that abiraterone steroidal metabolites had an effect on steroid metabolism in LnCaP and AR target gene expression in LAPC4 cells. In the upcoming funding year, I will continue to investigate these effects and to study the effect of abiraterone steroidal metabolites on other steroids and other AR regulated genes in other prostate cancer cell lines. I also will analyze patient's samples and process the results to study the association of abiraterone steroidal metabolites with patient's characteristics.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?
Nothing to Report.

What was the impact on other disciplines?
Nothing to Report.

What was the impact on technology transfer?
Nothing to Report.

What was the impact on society beyond science and technology?
Nothing to Report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change
Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them
In this funding period we planned to analyze 80 subjects, however we were able to consent only 57 patients but only 36 started the treatment, this will make it difficult for our analysis. We anticipate that by the mid of next year we will have sufficient number of patients who started the treatment thus we can analyze the samples by LC-MS.

Changes that had a significant impact on expenditures
Nothing to Report

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

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

  Journal publications.
  Nothing to Report.

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

  Other publications, conference papers and presentations.
  Nothing to Report.

- **Website(s) or other Internet site(s)**
  Nothing to Report.

- **Technologies or techniques**
  Nothing to Report.

- **Inventions, patent applications, and/or licenses**
  Nothing to Report.

- **Other Products**
  Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS
What individuals have worked on the project?

Name: Mohammad Alyamani
Project Role: Principle Investigator
Researcher Identifier (e.g. ORCID ID): 0000-0002-7127-0820
Nearest person month worked: 12

Contribution to Project: Mohammad is responsible for design, perform and interpret experiments.
Funding Support:

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Nothing to Report.

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

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:
Nothing to Report.

QUAD CHARTS:
Nothing to Report.

9. APPENDICES:

- ***The Annual Award Chart***

Award Log Number: PC170561

Award Title: Abiraterone Steroidal Metabolites as Biomarkers for Treatment Resistance in Prostate Cancer

PI: Mohammad Alyamani, Cleveland Clinic Foundation, Ohio **Budget:** $257,472.60

Topic Area: DoD Prostate Cancer Research Program **Mechanism:** Early Investigator Research Award

Research Area(s): 0403 **Award Status:** 08/01/2018-07/31/2019

Study Goals:

Overall this project aims to investigate the steroidogenic metabolism of abiraterone and evaluate the role(s) of the metabolites in prostate cancer.

Specific Aims:

specific aim 1) Determine abiraterone metabolites in patients with metastatic castration-sensitive PCa and determine the relationships between metabolite levels and clinical outcomes.

specific aim 2) Analyze the activity of abiraterone metabolites to identify possible resistance mechanisms.

Key Accomplishments and Outcomes:

Publications: none to date

Patents: none to date

Funding Obtained: none to date