

AWARD NUMBERS: W81XWH-14-1-0554

TITLE: Development of Personalized Cancer Therapy for Men with Advanced Prostate Cancer

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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

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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE October 2017		2. REPORT TYPE Annual		3. DATES COVERED 09/22/2016-09/21/2017	
4. TITLE AND SUBTITLE Development of Personalized Cancer Therapy for Men with Advanced Prostate Cancer				5a. CONTRACT NUMBER N/A	
				5b. GRANT NUMBER W81XWH-14-1-0554	
				5c. PROGRAM ELEMENT NUMBER N/A	
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				5e. TASK NUMBER N/A	
				5f. WORK UNIT NUMBER N/A	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) The University of Texas University of Michigan MD Anderson Cancer Center 1400 E. Medical Center Drive 1515 Holcombe Blvd. Room 5316 CC Houston, TX 77030-4009 Ann Arbor, MI 48109-5940				8. PERFORMING ORGANIZATION REPORT NUMBER N/A	
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) N/A	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S) N/A	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT The purpose of this study is to develop a strategy to identify molecular markers of response of advanced prostate cancer to specific therapies using clinically relevant prostate cancer patient-derived xenografts (PDXs). The MD Anderson and Michigan teams will interact closely to analyze results and generate a responder ID profile hypothesis. The validity of the responder ID profiles will be assessed in clinical trials. When we were in the process of performing our studies at the MD Anderson site, we were informed that there was a miscommunication between MD Anderson and USAMRMC Animal Care and Use Review Office (ACURO) and that the animal protocols had not been reviewed by ACURO. Thus we were asked to stop all studies and to return all funds utilized for the project as this could not be executed until the animal protocol is approved by ACURO. In May 2016, we had our animal protocol approved and we started our studies. Since then we have made progress in identifying mechanisms of FGFR signaling response which will help select patients for FGFR blockade.					
15. SUBJECT TERMS Bone metastases, targeted therapy, prostate cancer					
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	UU	29	19b. TELEPHONE NUMBER (include area code)

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Development of Personalized Cancer Therapy for Men with Advanced Prostate Cancer

Annual Report

1. INTRODUCTION

Castration-resistant progression and bone metastasis are hallmarks of advanced prostate cancer, for which there is no cure. Recent clinical trials have had encouraging results but only in subsets of patients, and emergence of treatment resistance is inevitable for most patients. Thus, strategies for selecting patients who are responders to treatment and identifying effective combination treatment strategies are urgently needed. The purpose of this study is to develop a strategy for identifying molecular markers of response of advanced prostate cancer to specific therapies. To achieve this goal, we will use clinically relevant prostate cancer patient-derived xenografts (PDXs). We will identify genomic alterations in these PDXs. The MD Anderson and the Michigan Center for Translational Pathology (MCTP) teams will interact closely to analyze genomic analysis results to generate a responder ID profile hypothesis. The validity of the responder ID profiles will be assessed in clinical trials.

2. KEYWORDS

Bone metastases, targeted therapy, prostate cancer.

3. ACCOMPLISHMENTS

What were the major goals of the project?

Specific Aim 1: Develop PDXs that reflect the lethal form of prostate cancer.

Major Task 1: Develop clinically relevant prostate cancer xenografts and comprehensively characterize the xenografts and human donor tumors.

Subtask 1: Establish new and expand existing prostate cancer PDXs from bone metastases or primary tumors. **(1-24 months, Dr. Nora Navone)**

Subtask 2: Assess the histopathologic and immunohistochemical characteristics of the prostate cancer xenografts and human tumors of origin. **(1-20 months, Drs. Navone and Arul Chinnaiyan)**

- Select currently available and recently developed (subtask 1) PDXs derived from primary prostate cancer or bone metastases.
- Perform histopathologic and immunohistochemical characterization of selected prostate cancer PDXs.
- Assess the fidelity of the prostate cancer PDXs to the human tumors of origin.

Specific Aim 2: Develop a responder ID profile hypothesis according to the treatment responsiveness of fully characterized prostate cancer PDXs.

Major Task 2: Identify prostate cancer PDX responders and nonresponders (primary resistance) to treatment with specific drugs and establish treatment-resistant PDX lines.

Subtask 1: Identify prostate cancer PDX responders and nonresponders (primary resistance) to abiraterone plus enzalutamide and establish lines of PDXs resistant to abiraterone plus enzalutamide (acquired resistance). **(1-24 months, Dr. Navone)**

Subtask 2: Identify prostate cancer PDX responders and nonresponders (primary resistance) to cabozantinib and develop cabozantinib-resistant PDX lines (acquired resistance). **(1-24 months, Dr. Chinnaiyan)**

Subtask 3: Identify prostate cancer PDX responders and nonresponders (primary resistance) to dovitinib and develop dovitinib-resistant PDX lines (acquired resistance). **(1-24 months, Dr. Navone)**

Major Task 3: Perform integrative genomic analysis of responder and primary and secondary treatment-resistant prostate cancer PDXs.

Subtask 1: Send flash-frozen specimens of responder and primary and secondary treatment-resistant prostate cancer PDXs and normal DNA obtained from human donor tumors to the MCTP for whole-genome and transcriptome sequencing (RNA-seq) and for targeted whole-exome sequencing. **(8-24 months, Drs. Chinnaiyan, Dan Robinson, and Yi-Mi Wu)**

Subtask 2: Perform data analysis to identify a list of genomic alterations deemed clinically relevant. **(12-24 months, Drs. Chinnaiyan, Robinson, and Wu)**

Subtask 3: Identify potential pathways of resistance that can be targeted in combination trials based on clinically relevant genomic alterations in therapy-responsive and -resistant prostate cancer PDXs. **(12-24 months, Drs. Navone, John Araujo, Christopher Logothetis, Drs. Chinnaiyan, Robinson, and Wu)**

Subtask 4: Subject prostate cancer PDXs to therapies targeting pathways identified in subtask 3 in combination with abiraterone and enzalutamide, cabozantinib, or dovitinib, giving priority to drugs currently in prostate cancer clinical trials at MD Anderson or the University of Michigan. **(12-34 months, Drs. Navone and Chinnaiyan)**

Subtask 5: Generate a responder ID profile. This hypothesis proposes a link between therapy responses (responder or nonresponder) of prostate cancer PDXs and the identified clinically relevant genomic alterations. The hypothesis will be tested in Specific Aim 3. **(12-24 months, Drs. Navone, Araujo, Logothetis, Bradley Broom and Drs. Chinnaiyan, Robinson, and Wu)**

Specific Aim 3: Validate the responder ID profile hypothesis in a clinical trial.

Major Task 3: Test this hypothesis by analyzing bone biopsy specimens and/or bone marrow aspirates obtained from sites with bone metastases in patients enrolled in the clinical studies listed in the grant.

Subtask 1: Assess the presence of genomic alterations that define the responder ID profile hypothesis in FFPE bone marrow core biopsy specimens and/or bone marrow aspirates (soluble fractions) obtained before and/or after 8 weeks of treatment. **(24-34 months, Drs. Navone, Araujo, Logothetis, Patricia Troncoso, Broom, and Drs. Chinnaiyan, Robinson, and Wu)**

- Abiraterone and enzalutamide clinical study (NCT01650194; PI: CJ Logothetis). Three arms: enzalutamide combined with abiraterone (n=20), enzalutamide (n=20), and abiraterone (n=20).
- Cabozantinib clinical study (NCT00940225; PI: P Corn at MD Anderson). N=21.
- Dovitinib clinical study (NCT00831792; PI: P Corn). N=40.

Subtask 2: Examine the results of the bone biopsy specimen and/or bone marrow aspirate analysis (performed by our collaborating statistician, Dr. Broom, in a close interaction with **Drs. Navone, Logothetis, Araujo, Troncoso, and Chinnaiyan**) to determine whether the patients' responses to therapy were predicted by our responder ID profile hypothesis. (24-34 months)

What was accomplished under these goals?

Major Task 1. As previously mentioned, when we were in the process of performing our studies at the MD Anderson site, we were informed that there was a miscommunication between MD Anderson and USAMRMC Animal Care and Use Review Office (ACURO) and that the animal protocols had not been reviewed by ACURO. Thus we were asked to stop all studies and return all funds utilized thus far for the project as this could not be executed until the animal protocol is approved by ACURO. In May 2016, we had our animal protocol approved and we started our studies. We thus started the establishment of new PDXs derived from the prostate and bone metastases. **Table 1** outlines the tumor tissue implanted in mice for PDX development since May 2016. Table 1 was also presented in the Progress Report 2016 but now we have updated this table to reflect the current Passage of all tissue implanted and new cases implanted in mice since September 2016 (MD Anderson site, Dr. Navone's Laboratory). The PDXs in passages 3 to 5 will be sent to Dr. Chinnaiyan laboratory for genomic characterization.

The specific objective is to have a panel of PDXs that would reflect human prostate cancer so that they can be utilized for our preclinical studies. However, given that PDXs derived from prostate cancer have a slow growth rate. For the proposed studies, we will use PDX previously established in our laboratory. Nevertheless, we will continue to develop PDXs and these PDXs will also be made available to the scientific community through a material transfer agreement.

We have selected prostate cancer PDXs derived bone metastases (MDA PCa 118b and MDA PCa 183) and primary prostate cancer (MDA PCa 180-30 and MDA PCa 149-1) for which we have assessed the fidelity with the human tumor of origin. We will utilize these lines in the first preclinical studies. We will continue the characterization with the newly established lines.

Table 1. Prostate Cancer Tissue Specimen Implanted into Mice for PDX Developed Since May 2016								
Date of tissue implantation in mice	Patient Number	Clinical Stage	Human Donor Tumor Information			PDX Information		
			Procedure Type	Pathology Diagnosis	Tumor Site	PDX Name (MDA PCa)	Current Passage	PSA
5/23/16	327	Metastatic	Biopsy	Metastatic adenocarcinoma	Bone marrow	327-1	stop growing/Failed	
			Venipuncture	N/A	CTC	327-2	2	
6/9/16	328	Primary	Venipuncture	N/A	CTC	328-0	stop growing/Failed	
			Transurethral Resection	Small cell carcinoma with neuroendocrine differentiation	Prostate	328-1	stop growing/Failed	
						328-3	4	79
						328-5	3	
7/5/16	329	Primary	Radical Prostatectomy	Adenocarcinoma	Prostate	329-9	2	
7/20/16	330	Metastatic	Biopsy-Core	Metastatic adenocarcinoma	Bone	330-A	stop growing/Failed	

Date of tissue implantation in mice	Patient Number	Clinical Stage	Human Donor Tumor Information			PDX Information		
			Procedure Type	Pathology Diagnosis	Tumor Site	PDX Name (MDA PCa)	Current Passage	PSA
7/29/16	331	Metastatic	Biopsy-Core	Atypical cells	Bone	331-A	stop growing/Failed	
8/17/16	332	Metastatic	Biopsy-Core	Carcinoma	Liver	332-B	stop growing/Failed	
9/2/16	333	Locally Advanced	Resection	Adenocarcinoma	Soft tissue	333-1	2	
9/2/16	334	Metastatic	Venipuncture	N/A	CTC	334-1	stop growing/Failed	
9/9/16	335	Metastatic	Venipuncture	N/A	CTC	335-1	stop growing/Failed	
9/13/16	336	Locally Advanced	Biopsy-Core	Adenocarcinoma	Soft tissue	336-A	stop growing/Failed	
10/3/16	337	Metastatic	Biopsy-Core	Metastatic carcinoma with neuroendocrine differentiation	Liver	337-A	4	62
10/11/16	338	Metastatic	Biopsy-Core	Metastatic adenocarcinoma	Bone	338-B	stop growing/Failed	
10/11/16	339	Metastatic	Biopsy-Core	Metastatic adenocarcinoma	Lymph node	339-A	stop growing/Failed	
10/14/16	340	Metastatic	Biopsy-Core	Metastatic carcinoma	Bone	340-A	stop growing/Failed	
10/17/16	341	Metastatic	Biopsy-Core	Metastatic adenocarcinoma	Pelvic lymph node	341-A	stop growing/Failed	
		Metastatic	Biopsy-Core	Metastatic Adenocarcinoma	Pelvic lymph node	341-B	stop growing/Failed	
10/19/16	342	Metastatic	Biopsy-Core	Malignant epithelioid and spindle cell neoplasm with osteoid differentiation	Pelvic soft tissue	342-B	5	41
10/26/16	343	Metastatic	Biopsy-Core	Metastatic adenocarcinoma	Retroperitoneal lymph node	343-A	stop growing/Failed	
11/18/16	344	Metastatic	Venipuncture	N/A	Blood	344-A	stop growing/Failed	
12/12/16	345	Metastatic	Biopsy-Core	Metastatic Adenocarcinoma	Para-aortic lymph node	345-A	stop growing/Failed	
12/20/16	346	Metastatic	Biopsy-Core	Metastatic moderately differentiated adenocarcinoma	Liver	346-A	1	
1/20/17	347	Metastatic	Biopsy-Core	Metastatic high grade adenocarcinoma	Liver	347-A	stop growing/Failed	
		Metastatic	Biopsy-Core	Metastatic high grade adenocarcinoma	Liver	347-B	stop growing/Failed	
1/27/17	348	Locally Recurrent	Transurethral Resection	High grade adenocarcinoma	Bladder	346-1 and 3	stop growing/Failed	
2/3/17	349	Metastatic	Biopsy-Core	Metastatic poorly differentiated carcinoma	Adrenal gland	349-A and -B	Implanted	
2/6/17	350	Metastatic	Biopsy-Core	Poorly differentiated malignant neoplasm	Prostate	350 a+B	3	
2/7/17	351	Metastatic	Biopsy-Core	Metastatic adenocarcinoma	Liver	351-A and -B	Implanted	
2/10/17	352	Metastatic	Lymph Node Dissection	Metastatic Adenocarcinoma	Lymph node	352-1	1	
			Lymph Node Dissection	Metastatic Adenocarcinoma	Lymph node	352-8	1	
			Lymph Node Dissection	Metastatic Adenocarcinoma	Lymph node	352-14	1	

Date of tissue implantation in mice	Patient Number	Clinical Stage	Human Donor Tumor Information			PDX Information		
			Procedure Type	Pathology Diagnosis	Tumor Site	PDX Name (MDA PCa)	Current Passage	PSA
2/17/17	353	Metastatic	Biopsy-Core	Metastatic adenocarcinoma	Lymph node	353 A+B	Implanted	
2/27/17	354	Metastatic	Lymphadenectomy	Metastatic adenocarcinoma	Lymph node	354-3	Implanted	
			Lymphadenectomy	Metastatic adenocarcinoma	Lymph node	354-5	Implanted	
			Lymphadenectomy	Metastatic adenocarcinoma	Lymph node	354-7	Implanted	
3/14/17	355	Metastatic	Cystectomy	Adenocarcinoma with predominately sarcomatoid and small cell components	Rectum	355-3	4	
			Cystectomy	Adenocarcinoma with predominately sarcomatoid and small cell components	Rectum	355-6	4	
			Cystectomy	Adenocarcinoma with predominately sarcomatoid and small cell components	Bladder	355-9	3	
			Cystectomy	Adenocarcinoma with predominately sarcomatoid and small cell components	Bladder	355-12	3	
			Cystectomy	Adenocarcinoma with predominately sarcomatoid and small cell components	Lymph node	355-15	4	
			Cystectomy	Adenocarcinoma with predominately sarcomatoid and small cell components	Lymph node	355-18	4	
4/4/17	356	Metastatic	Lymph Node Dissection	Metastatic adenocarcinoma	Lymph node	356-3	Implanted	
4/18/18	357	Locally Advanced	Resection	adenocarcinoma	Pelvic mass	357-1	Implanted	
4/25/17	358	Metastatic	Bone Marrow Biopsy	No tumor present	Bone marrow	358-A	Implanted	
5/2/17	359	Metastatic	Prostatectomy	Adenocarcinoma	Prostate	359-11	Implanted	
5/4/17	360	Locally Advanced	Prostatectomy	Adenocarcinoma	Prostate	360-15	Implanted	
6/12/17	361	Metastatic	Venipuncture	N/A	Blood	361A + B	Implanted	
6/12/17	362	Metastatic	Biopsy-Core	Atypical Cells and Stromal Fibrosis	Prostate	363A+B	Implanted	
7/14/17	363	Primary	Prostatectomy	Adenocarcinoma	Prostate	363-10	Implanted	
8/25/17	364	Metastatic	Craniotomy	Pending	brain	364-1	Implanted	
			Craniotomy	Pending	brain	364-5	Implanted	
CTC: Circulating tumor cells. Notes: Cells highlighted in grey indicate implanted tissue that failed to grow. Highlighted areas in blue indicate PDXs in different passages. Not highlighted cells indicate recently implanted tissue that has not shown evidence of grow yet.								

Major Task 2: Under this task our objective is to identify prostate cancer PDX responders and nonresponders (primary resistance) to treatment with specific drugs and establish treatment-resistant PDX lines.

Subtask 2: Identify prostate cancer PDX responders and nonresponders (primary resistance) to cabozantinib and develop cabozantinib-resistant PDX lines (acquired resistance).

Subtask 3: Identify prostate cancer PDX responders and nonresponders (primary resistance) to dovitinib and develop dovitinib-resistant PDX lines (acquired resistance) (MD Anderson, Dr. Navone Laboratory).

The impetus for the studies with Dovitinib (Novartis Pharma), a FGFR inhibitor, was that Dovitinib demonstrated antitumor activity in a clinical study of men with prostate cancer (*Sci Transl Med* 6(252):252ra122, 2014). However, Dovitinib was withdrawn and a pan-FGFR kinase inhibitor, which is currently in a clinical phase I trial (NVP-BGJ398; Novartis Pharmaceuticals), is the lead compound being tested as anticancer therapy by Novartis. In addition, in an agreement with Janssen Pharmaceutical Companies of Johnson & Johnson we obtained a pan-FGFR inhibitor from (JNJS 42756493) to test in a preclinical setting.

Prior to May 2016 (before the ACURO review was in place), we tested the antitumor activity of JNJS 42756493 and NVP-BGJ398 against prostate cancer PDXs growing in bone. For this we used MDA PCa 118b PDX because they were responders in the study conducted using Dovitinib. We found that JNJS 42756493 (but not NVP-BGJ398) had antitumor activity against MDA PCa 118b PDX growing in the bone of mice. These results were outlined in our previous progress report, but we had to stop the studies and funds supporting these studies had to be restored to DOD until ACURO was reviewed and approved. At that time, we had initiated a second preclinical study treating MDA PCa 118b growing in the bone of mice with JNJS 42756493 with the goal of setting aside tissue samples for comprehensive genomic analyses and will also develop resistant lines. We now are requesting approval from DOD to use JNJS 42756493 in our studies instead of Dovitinib because, as we mentioned, Dovitinib is not available anymore for clinical studies and JNJS 42756493, which is currently used in our Department to treat men with bladder cancer, is the FGFR inhibitor with the most potent antitumor activity of the ones we tested.

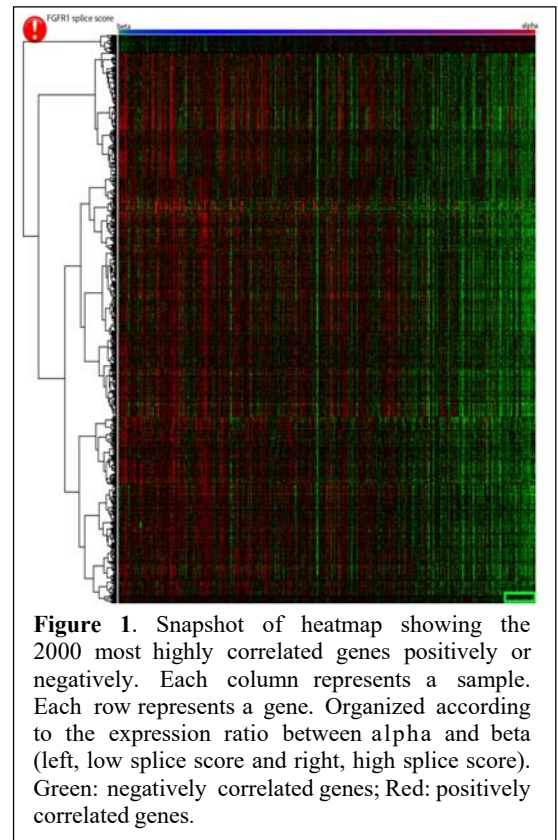
Major Task 3: Perform integrative genomic analysis of responder and primary and secondary treatment-resistant prostate cancer PDXs (University of Michigan, Dr. Chinnaiyan Laboratory, and MD Anderson, Dr. Navone Laboratory).

Subtask 1: As mentioned in the previous progress report (Progress report 2016), Dr. Arul Chinnaiyan at the University of Michigan assessed expression levels of FGFR1 transcripts by RNA sequencing of 183 human prostate cancer samples and of PDXs. The length of the protein isoforms related to the predicted transcripts, found by RNA sequencing, range between 731 to 853aa. When performing the analysis, we identified eight different protein coding transcript to be the most abundantly expressed, (with a predicted protein length of 820 to 853aa); probably reflecting FGFR1alpha and FGFR1 beta isoforms (**Table 2**). The studies presented here will thus focus in these two best-characterized isoforms. Also published in previous progress report, we found that all PDXs express primarily FGFR1alpha isoform while prostate cancer cell lines express.

Most abundant expressed transcripts	Predicted protein length
ENST00000326324 ENST00000356207 ENST00000397103	731-733 aa
ENST00000397091 ENST00000397108 ENST00000397113 ENST00000425967 ENST00000532791	820-853 aa

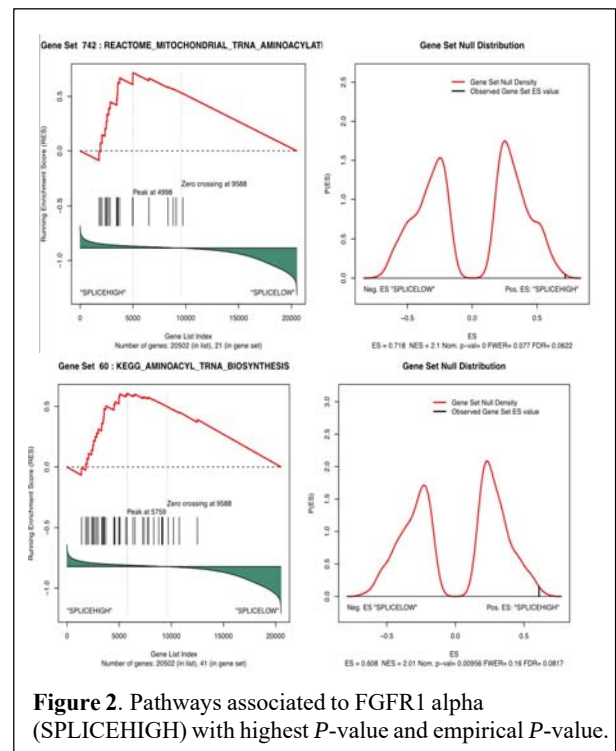
Table 2. Different prostate cancer tissue samples express different FGFR1 isoforms. RNA sequencing analysis of FGFR1 transcripts in human prostate cancer samples and PDXs (performed in collaboration with Dr. Arul Chinnaiyan, MCTP).

In collaboration with Bradley Broom (Professor, Department of Bioinformatics and Computational Biology), we mined the human RNA sequencing data from TCGA for expression of FGFR1 isoforms and its molecular and clinical correlates. The search was performed using the specific sequence of each of the FGFR1 isoforms, alpha and beta. To perform the analyses, an FGFR1 splice score was defined as the ratio between FGFR1 alpha versus FGFR1 beta. A high FGFR1 score indicates prevalence of FGFR1 alpha and a low FGFR1 score indicates prevalence of FGFR1 beta. We subsequently assessed the expression of genes and pathways associated to FGFR1 splice score. **Figure 1** is a heatmap showing the top 2000 genes positively or negatively correlated with the FGFR1 splice score. In Figure 1, two patterns of expression are observed being more the genes that are negatively correlated (highly correlated with isoform beta) than positively correlated (highly correlated with isoform alpha) with the FGFR1 splicing score. Then, we evaluated the 20 most correlated genes with FGFR1 splice score. Among the genes with highest correlation to FGFR1 splice score, Calcium-Activated Nucleotidase 1 (CANT1) and UDP-N-Acetylglucosamine Pyrophosphorylase 1 (UAP1) could be of further interest, because they are highly expressed in prostate cancer and are androgen regulated (7-9). On the other hand, none of the 20 genes mostly correlated to the beta isoform (lowest correlation) has been previously associated with prostate cancer. Nevertheless, we observe that the fold-change in correlation for the group of genes related to alpha is weak (i.e. around 0.3) and for beta, medium (i.e. around 0.5). So, we decided to focus on the pathways associated to FGFR1 splice score.



We then identified pathways correlated with FGFR1 splice score. Since many pathways are associated with FGFR1 splice score with a statistical significant P value (particularly true for pathways associated with beta isoform (approximately 750 pathways)), we decided to prioritize those pathways with a P -value < 0.002 and an observed gene set enrichment score (ES) value falling the furthest from a random distribution (empirical P value). Under these criteria we found two alpha associated pathways, namely mitochondrial tRNA aminoacylation and aminoacyl tRNA biosynthesis with a p -value < 0.002 and $= 0.00956$, respectively (**Figure 2**).

With respect to the pathways associated to FGFR1 beta isoform, at first glance, many are immune system related pathways. Using the P -value < 0.002 value and the empirical P value criteria, we found of



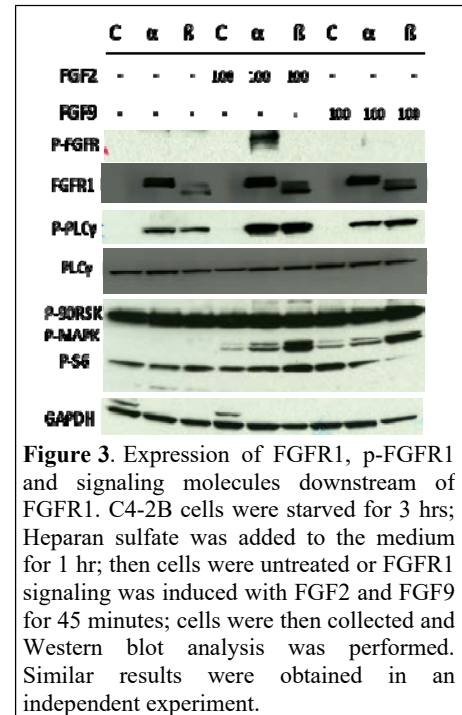
particular interest the MAPK signaling cascade, signaling by FGFR in disease, and pathways in cancer are significantly correlated with FGFR1 beta (but not alpha) isoform (i.e., low FGFR1 splice score).

With respect to the clinical correlates of FGFR1 splice score, unfortunately, there is a limited amount of cases with the highest or lowest FGFR1 splice score; in these few samples, a correlation between FGFR1 score and recurrence parameters is found. One parameter left to analyze is plotting parameters of recurrence and non-recurrence related to FGFR1 splice score.

Expression of FGFR1 isoforms alpha and beta in prostate cancer cells results in different molecular outcomes.

We developed C4-2B prostate cancer cells stably expressing a bicistronic vectors containing FGFR1 isoforms and green fluorescent protein (GFP) (GenScript). Stable lines were developed by batch transfection and selection with gentamicin followed by cell sorting of GFP positive cells. The same procedure was used for the selection of all three C4-2B sublines (control empty vector, FGFR1 alpha and FGFR1 beta). Using these cells, we assessed the signaling pathways activated by FGFs.

Figure 3 illustrates our findings that phosphorylation of FGFR1 occurs only in cells expressing the alpha isoform. To detect FGFR1 phosphorylation, we use an antibody that recognizes Tyr653/654. These phosphorylation sites are important for catalytic activity of activated FGFR and are essential for signaling. Nevertheless, seven tyrosine residues in the cytoplasmic tail of FGFR1 can be phosphorylated: Tyr463, 583, 585, 653, 654, 730, and 766. These phosphorylated tyrosine residues may provide docking sites for downstream signaling components such as Crk and PLC γ . On the other hand, we observe significant higher phosphorylation of MAPK (p42/44) in cells expressing the beta isoform compared to alpha. These results are in agreement with our in silico findings that the MAPK cascade is significantly associated with the beta isoform.



Based on these studies, we hypothesize that FGFR1 alpha and beta confers different phenotypes to prostate cancer cells and this may underlay, at least in part, prostate cancer heterogeneity, pattern of progression, and differences of response to FGFR1 inhibitor.

Currently there are no commercially available isoform specific antibodies that work in clinical samples. Thus, we develop antibodies to recognize FGFR1 alpha and beta isoforms to identify clinical correlates in clinical specimens and develop tools to select PDXs (and subsequently men) putative responders to FGFR blockade. To that end to get an antibody that recognizes FGFR1 alpha isoform, we have designed a peptide (aa 31 to 59) that includes the sequence encoding the Ig-like domain in FGFR1 alpha not present in FGFR1 beta isoform (Ig I). To develop an antibody that recognizes FGFR1 beta isoform, we have designed a peptide (aa 21 to 41) that spans between the signal peptide and Ig II (a sequence that does not include Ig I) (**Figure 1**). The sequence was selected based on sequences blast (NCBI) and 3D structure modelling performed by Creative Biolabs (Upton, NY). The peptide was used to develop FGFR1 isoform specific mouse antibodies using hybridoma technology by Creative Biolabs.

We have initially tested the specificity and sensitivity of these antibodies by immunocytochemistry and western blot analyses of prostate cancer cells expressing empty vector, FGFR1 isoform alpha or beta.

Thus far the antibodies did not show isoform specificity. We are currently optimizing a protocol of cell preparation to perform the screening in a scenario closer to the final aim of use of these antibodies in formalin fixed paraffin embedded tissue samples (i.e. immunohistochemistry by fixing cell pellets and embedding them in paraffin).

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

Estefania Labanca

How were the results disseminated to communities of interest?

Oral presentation. Targeting the bone compartment in metastatic prostate cancer, 2nd Fibroblast Growth Factors in Development and Repair Conference, Cancun, Mexico, 3/2017

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

The PDXs in passages 3 to 5 will be sent to Dr. Chinnaiyan laboratory for genomic characterization and will be characterized by immunohistochemistry.

Given our results suggesting that FGFR isoforms mediate a different phenotype in prostate cancer, we will develop two prostate cancer cell lines (C4-3B and PC3) stably expressing FGFR1 alpha and beta isoforms. We will then assess the response of these cells to JNJS 42756493. We will also study whether FGFR1 alpha and beta isoforms changes the metastatic potential of the cells and whether JNJS 42756493 can inhibit metastases.

We will study the expression of FGFR1 alpha, beta in clinical samples reflecting the progression of the disease. We will then study the correlation of FGFR1 isoforms expression with the stage of prostate cancer (untreated versus CRPC, primary tumors versus metastases). We have previously tested commercially available FGFR1 isoform specific antibodies but they lack specificity at the immunohistochemistry assay. Thus, to test expression of FGFR1 isoforms we will perform RNA in situ hybridization (ISH) in archived samples (formalin fixed, paraffin embedded) in collaboration with Dr. Nallasivam Palanisamy (Henry Ford Health System, Detroit MI) who has extensive experience in performing RNA-ISH in clinical samples.

We will identify potential pathways of resistance that can be targeted in combination trials based on clinically relevant genomic alterations in therapy-responsive and -resistant prostate cancer PDXs.

4. IMPACT

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

We have established a series of PDXs that will be made available to the scientific community for research.

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**

We request approval for using JNJS 42756493 instead of dovitinib because Dovitinib is no longer available. We request approval for inject (intracardiacally and in the bone) male SCID mice with PC3 and C4-2B cells stably transfected with FGFR1 alpha, beta and empty vector. The protocols are approved in MD Anderson IACUC.

Actual or anticipated problems or delays and actions or plans to resolve them**Changes that had a significant impact on expenditures**

There was a miscommunication between MD Anderson and USAMRMC Animal Care and Use Review Office (ACURO) and that the animal protocols had not been reviewed by ACURO. Thus we were asked to stop all studies and to return all funds utilized thus far for the project as this could not be executed until the animal protocol is approved by ACURO. In May 2016, we had our animal protocol approved and we started our studies. As a result, we had a significant delay in the initiation of our studies and a positive balance in our budget that we request to carry forward to the next budget period. We have requested a 12-month no-cost extension to compensate for the delay.

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

We will use NJS 42756493 instead of dovitinib in in vivo studies. We request approval for inject (intracardiacally and in the bone) male SCID mice with PC3 and C4-2B cells stably transfected with FGFR1 alpha, beta and empty vector. The protocols are approved in MD Anderson IACUC.

Significant changes in use or care of human subjects

No changes

Significant changes in use or care of vertebrate animals

No changes

Significant changes in use of biohazards and/or select agents

No changes

6. PRODUCTS

Publications, conference papers, and presentations

Oral and Poster presentation at Navone, NM. Targeting the bone compartment in metastatic prostate cancer, 2nd Fibroblast Growth Factors in Development and Repair Conference, Cancun, Mexico, 3/2017

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

Development of PDXs that will be made available to the scientific community.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

The University of Texas MD Anderson Cancer Center

Name:	Nora M. Navone
Project Role:	Principal Investigator
Nearest person month worked:	1.80 calendar months
Contribution to Project:	Dr. Navone is responsible for designing the experiments, evaluating the results, coordinating the personnel's efforts related to all in vivo studies in mice, and preparing prostate cancer cells derived from human prostate cancer xenografts. She closely interacts with Dr. Chinnaiyan to integrate the research efforts within this project.
Funding Support:	Funding support is provided from this award.

Name:	John Araujo
Project Role:	Co-Principal Investigator
Nearest person month worked:	0.12 calendar months
Contribution to Project:	Dr. Araujo provides clinical data on the follow-up of men whose prostate cancer was the source of prostate cancer xenografts or was a tissue specimen used for genomic analysis. He works closely with Dr. Navone in the analysis of these data and their correlation with molecular studies.
Funding Support:	Funding support is provided from this award.

Name:	Bradley Broom
Project Role:	Collaborator
Nearest person month worked:	0.24 calendar months
Contribution to Project:	Dr. Broom provides expertise in biostatistics to analyze the data emerging from the preclinical studies, including the molecular studies, and relate them to the findings emerging from the clinic.
Funding Support:	Funding support is provided from this award.

Name:	Estefania Labanca
Project Role:	Graduate Research Assistant-GSBS
Nearest person month worked:	3.60 calendar months
Contribution to Project:	Upon Xinhai Wan's departure from the department, Ms. Labanca will be responsible for intrabone injection of prostate cancer cells in mice and the in vivo experiments involving laboratory animals. She will perform the immunohistochemical studies of tissue samples and the molecular and cell biology studies related to the in vivo studies. Dr. Wan trained her in these techniques before he left.
Funding Support:	Salary support will be provided from this grant upon DOD approval.

Name:	Jun Yang
Project Role:	Research Laboratory Coordinator
Nearest person month worked:	3 calendar months
Contribution to Project:	Ms. Wang is responsible for preparing cell and tumor lines for the planned experiments and for performing assays involving molecular and cell biology techniques. She also provides technical support for the experiments involving in vivo manipulation of animals and will order supplies.
Funding Support:	Funding support is provided from this award.

The University of Michigan

Name:	Arul Chinnaiyan
Project Role:	Partnering PI
Nearest person month worked:	0.60 calendar months
Contribution to Project:	Responsible for overall oversight of the project and co-directs the CLIA-certified lab. He is accountable that the project produces high quality data and coordinates the efforts of the personnel and collaborators. He closely interacts with Dr. Navone to integrate the research efforts within this project.
Funding Support:	He receives salary from the Howard Hughes Medical Institute.

Name:	Dan Robinson
Project Role:	Co-Investigator
Nearest person month worked:	1.92 calendar months
Contribution to Project:	Oversees preparation of sequencing libraries, quality control, and provides expertise in genome biology.
Funding Support:	Funding support is provided from this award.

Name:	Yi-Mi Wu
Project Role:	Co-Investigator
Nearest person month worked:	3.60 calendar months
Contribution to Project:	Guide the project's research development and facilitate interpretation of sequence data.
Funding Support:	Funding support is provided from this award.

Name:	Xiaoxuan Dang
Project Role:	Sequencing Technician
Nearest person month worked:	3.0 calendar months
Contribution to Project:	Assisting in library generation and sequencing.
Funding Support:	Funding support is provided from this award.

Name:	Robert Lonigro
Project Role:	Bioinformatics Analyst
Nearest person month worked:	0.6 calendar months
Contribution to Project:	Provides bioinformatic analysis in the context of candidate gene nominations.
Funding Support:	Funding support is provided from this award.

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

Yes, the active other support for key personnel has changed. Several grants have expired and new ones have been awarded. We are including the updated active other support below for key personnel.

MD ANDERSON KEY PERSONNEL

NAVONE, Nora

CURRENT

Prostate Moon Shot Title:	(Logothesis/Giancotti) Prostate Cancer Moon Shot Flagship 1: Optimizing AR Signaling Inhibition and Addressing Mechanisms of Resistance
Time Commitments:	1.20 calendar
Supporting Agency:	MD Anderson Moon Shot Program
Grants Officer:	Carrie C. Feighl, Director, Research Finance, Phone: 713-792-3477 cfeighl@mdanderson.org

Performance Period: 09/01/2017-08/31/2018
 Level of Funding:
 Goals: The emphasis is on developing new therapeutic approaches targeting tumor cell-intrinsic mechanisms. The overarching goal is to rationally integrate such approaches with those targeting the immune microenvironment (FP2) and the non-immune microenvironment (FP3).
 Specific Aims:

- To design and implement innovative clinical trials based on an increased understanding of the tumor cell-intrinsic mechanisms driving tumor progression and resistance to AR-targeted agents.
- To identify mechanisms and biomarkers of response and resistance to agents that target oncogenic signaling pathways and/or non-oncogene dependencies, including lineage-dependent transcription factors and synthetic essential genes.
- To develop a personalized management of prostate cancer based on the evolving repertoire of genetic and epigenetic lesions driving disease progression on therapy.

 Role: Investigator

W81XWH-14-1-0554 (Navone)
Title: Development of Personalized Cancer Therapy for Men with Advanced Prostate Cancer

Time Commitments: 1.80 calendar
 Supporting Agency: DOD-PCRP Synergistic Idea Development Award
 Grants Officer Address: Janet P. Kuhns, Phone: 301-619-2827, janet.p.kuhns.civ@mail.mil
 Performance Period: 09/22/2014-09/21/2018 NCE
 Level of Funding:
 Goals: To develop a strategy for using integrative genomic analysis of prostate cancer patient derived xenografts (PDXs) to facilitate biomarker-driven clinical trials. Over the long term, we expect our approach to improve upon the strategy for testing therapeutic agents for prostate cancer, aid in patient care, and facilitate the development of personalized therapies for prostate cancer.
 Specific Aims: 1. Develop PDXs that reflect the lethal form of prostate cancer. 2. Develop a responder ID profile hypothesis according to the treatment responsiveness of fully characterized prostate cancer PDXs. 3. Validate the responder ID profile hypothesis in a clinical trial.
 Role: Principal Investigator

Janssen (Navone)
Title: FGFR Inhibitors in Prostate Cancer Bone Metastasis
 Time Commitments: 1.80 calendar
 Supporting Agency: Janssen Research and Development
 Grants Officer Address: James Bischoff, Sr. Director, Phone: 215-628-5971, jbischol@its.jnj.com
 Jhilik De, Administrative Contact, Jde5@its.jnj.com
 Performance Period: 08/14/2014-07/31/2019
 Level of Funding:
 Goals: This program's goal is to test the antitumor efficacy of a pan-FGFR inhibitor against patient-derived xenografts developed in my laboratory.

Specific Aims: 1. Assess the efficacy of pan FGFR inhibitor(s) (company material) on prostate cancer PDX growing in the bone of male SCID mice. 2. Assess the efficacy of company material on the growth of prostate cancer PDX in bone of male SCID mice. 3. Screen tissue microarrays (TMAs) containing prostate cancer PDXs for expression of targets of interest to company.

Role: Principal Investigator

R01 CA193362-01A1 (Yang)
Title: Role of Integrin VLA-6 in Suppression of Bone Formation in Myeloma

Time Commitments: 0.60 calendar

Supporting Agency: NIH/NCI

Grants Officer Address: LeSchell D. Browne, Phone: 240-276-5432, leschell.browne@nih.gov

Performance Period: 02/01/2016-01/31/2021

Level of Funding:

Goals: The goal of this project is to investigate the mechanism by which myeloma cells alter the balance of adipogenesis and osteoblastogenesis, thereby suppressing bone formation.

Specific Aims: 1. Determine whether the $\alpha 6$ integrin in myeloma cells enhances adipogenesis and suppresses osteoblastogenesis and bone formation. 2. Determine whether $\alpha 6$ in myeloma cells binds to its ligand in MSCs to activate a signaling pathway(s) that enhances adipocyte and inhibits osteoblast differentiation.

Role: Co-Investigator

2 P50 CA140388-07 (Logothetis/Thompson)
Title: MD Anderson Cancer Center Prostate Cancer SPORE
Core 2: Biospecimen and Pathology Core

Time Commitments: 0.60 calendar

Supporting Agency: NIH/NCI

Grants Officer Address: Martinson Owusu, Phone: 240-276-6297, owusumo@mail.nih.gov

Performance Period: 09/01/2016-08/31/2021

Level of Funding:

Goals: The goal of this Core is to provide the infrastructure, biorepository, xenograft facility, pathological and technical expertise, and informatic infrastructure required to support the projects of the MD Anderson Prostate Cancer SPORE and ensure the achievement of their goals.

Specific Aims: 1. Collect, process, annotate, characterize, store, and distribute human biospecimens related to prostate cancer. 2. Create well-characterized and quality-controlled tissue derivatives (including PDXs) for translational research and conduct selected tissue-based studies. 3. Provide investigators with expertise to optimally select and use biospecimen resources, analytical techniques, and interpretation of tissue-based studies. 4. Provide an informatics solution that tightly integrates biospecimen acquisition, annotation, and analysis workflows with clinical data in a secure and accessible manner.

Role: Co-Investigator, Core 2

2013-0933

Title:

(Araujo)

An Observation, Open Label Study of Alpharadin (Radium 223) in Patients with Castrate Resistant Prostate Cancer Bone Metastases

Time Commitments:

0.0 calendar

Supporting Agency:

Bayer

Performance Period:

07/02/2016-12/31/2018

Level of Funding:

Goals:

This is an open label study to determine the effect of Alpharadin on the bone marrow microenvironment in patients with castrate resistant prostate cancer (CRPC) and bone metastases. We will determine the modulation of bone microenvironment as measured by serum, plasma, urine and bone marrow aspirate bone markers.

Specific Aims:

The primary objective is to identify markers of both predictive and prognostic importance within bone marrow biopsies, aspirates as well as serum in patients with metastatic CRPC to bone, to be treated with the standard 6 doses of Alpharadin. The secondary objectives are:

1. link prostate specimen antigen initial concentration to modulation of bone markers, in the blood, urine, and bone marrow plasma of study patients. 2. estimate the efficacy and progression free survival by PCWG2 in study patients. 3. develop a deeply annotated tissue repository for later hypothesis generating associations. 4. to estimate the overall survival in patients with CRPC.

Role:

Co-Investigator

Movember Action Plan (Navone)

Title:

Initiative: GAP1 Xenograft Project Integration Plan: Development of Prostate Cancer Xenografts to Model Human Prostate Cancer

Time Commitments:

0.12 calendar

Supporting Agency:

PCF/Movember

Grants Officer Address:

Audrey Gardner, Manager of Program Administration, Phone: 310-570-4792

agardner@pcf.org

Performance Period:

01/01/2014-Ongoing collaboration

Level of Funding:

\$0 annual direct. No additional funds to be awarded after 12/30/2016.

Goals:

The ultimate goal of this project is to create a catalog of prostate cancer PDXs developed in different institutions around the world. This catalog would contain basic information of the prostate cancer PDXs associated to expression of genes most frequently altered in prostate cancer as assessed by immunohistochemical analyses of tissue microarrays.

Specific Aims:

Not applicable

Role:

Principal Investigator

OVERLAP: None

ARAUJO, John

CURRENT

W81XWH-14-1-0554

(Navone)

Title:

Development of Personalized Cancer Therapy for Men with Advanced Prostate Cancer

Time Commitments: 0.12 calendar
 Supporting Agency: DOD-PCRP Synergistic Idea Development Award
 Grants Officer Address: Janet P. Kuhns, Phone: 301-619-2827, janet.p.kuhns.civ@mail.mil
 Performance Period: 09/22/2014-09/21/2018 NCE
 Level of Funding:
 Goals: To develop a strategy for using integrative genomic analysis of PDXs to facilitate biomarker-driven clinical trials. Over the long term, we expect our approach to improve upon the strategy for testing therapeutic agents for prostate cancer, aid in patient care, and facilitate the development of personalized therapies for prostate cancer.
 Specific Aims: 1. Develop PDXs that reflect the lethal form of prostate cancer. 2. Develop a responder ID profile hypothesis according to the treatment responsiveness of fully characterized prostate cancer PDXs. 3. Validate the responder ID profile hypothesis in a clinical trial.
 Role: Co-Investigator

2014-0026 (Araujo)
Title: A Phase 2 Study of Oral Selinexor (KPT-330) in Metastatic Castrate Resistant Prostate Adenocarcinoma

Time Commitment: 0 calendar
 Supporting Agency: Karyopharm Therapeutics
 Grant Officer Address: 85 Wells Ave., 2nd Floor, Newton, MA 02459
 Performance Period: 03/14/2014-06/30/2020
 Level of Funding:
 Amount depends on patient accrual for the year
 Project Goals: Our objective is to conduct a phase 2 study of oral selinexor (kpt-330) in metastatic castrate resistant prostate adenocarcinoma.
 Specific Aims: Not applicable
 Role: Principal Investigator

2 P50 CA140388-06A1 (Logothetis and Thompson)
Title: MD Anderson Cancer Center Prostate Cancer SPORE. Project 2: Targeting Tumor Microenvironment-induced Therapy Resistance in Prostate Cancer Bone Metastasis

Time Commitment: 0.60 calendar
 Supporting Agency: NIH/NCI
 Grants Officer: Leslie Hickman, Phone: 301-631-3009, hickmanl@mail.nih.gov
 Performance Period: 09/01/2016-08/31/2021
 Level of Funding:
 Project Goals: Our objectives are to develop strategies that can block osteocrine-mediated therapy resistance to enhance treatment efficacy.
 Specific Aims: 1. Examine the ability of osteocrines to confer therapy resistance through activation of FAK. 2. Examine the effects of second-generation FAK inhibitors (VS-6063 or VS-4718) on overcoming osteocrine-induced therapy resistance in xenograft mouse models. 3. Conduct a clinical trial to examine the toxicity and efficacy of a FAK inhibitor (VS-6063 or VS-4718) in men with treatment-refractory bone-metastatic castrate-resistant prostate cancer.
 Role: Clinical Co-Leader, Project 2

OVERLAP: None

BROOM, Bradley
CURRENT

5 P30 CA016672-40

Title:

Time Commitment:

Supporting Agency:

Grants Officer:

Performance Period:

Level of Funding:

Project Goals:

Specific Aims:

Role:

(Pisters)

Cancer Center Support Grant

4.68 calendar

NIH/NCI

Hasnaa Shafik, Program Director, Phone: 301-496-8531

shafikh@mail.nih.gov

07/01/2003-06/30/2018

The goal of this shared resource is to assist researchers in the application of state-of-the-art methodology for the development, conduct, and analysis of studies using high-throughput technologies. Effort added.

Same as above.

Co-Investigator

Prostate Moon Shot

Title:

Time Commitment:

Supporting Agency:

Grants Officer:

Performance Period:

Level of Funding:

Project Goals:

(Logothetis and Giancotti)

Prostate Cancer Moon Shot

Pilot Project 1: Optimizing AR Signaling Inhibition and Addressing Mechanisms of Resistance

1.20 calendar

MD Anderson Prostate Cancer Moon Shot Program

Carrie C. Feighl, Director, Research Finance, Phone: 713-792-3477

cfeighl@mdanderson.org

09/01/2017-08/31/2018

1. Design and implement innovative clinical trials based on an increased understanding of the tumor cell-intrinsic mechanisms driving tumor progression and resistance to AR-targeted agents. 2. Identify mechanisms and biomarkers of response and resistance to agents that target oncogenic signaling pathways and/or non-oncogene dependencies, including lineage-dependent transcription factors and synthetic essential genes. 3. Develop a personalized management of prostate cancer based on the evolving repertoire of genetic and epigenetic lesions driving disease progression on therapy. FP1's emphasis is on developing new therapeutic approaches targeting tumor cell-intrinsic mechanisms. The overarching goal is to rationally integrate such approaches with those targeting the immune microenvironment and the non-immune microenvironment.

Same as above

Bioinformatics Investigator

Specific Aims:

Role:

W81XWH-14-1-0554

Title:

Time Commitment:

Supporting Agency:

Grants Officer:

(Navone)

Development of Personalized Cancer Therapy for Men with Advanced Prostate Cancer

0.24 calendar

DOD-PCRP Synergistic Idea Development Award

Janet P. Kuhns, Contracting Officer, Phone: 301-619-2827

janet.p.kuhns.civ@mail.mil
 Performance Period: 09/22/2014-09/21/2018 NCE
 Level of Funding:
 Project Goals: The goal of this project is to develop a strategy for using integrative genomic analysis of prostate cancer PDXs to facilitate biomarker-driven clinical trials. Over the long term, we expect our approach to improve upon the strategy for testing therapeutic agents for prostate cancer, aid in patient care, and facilitate the development of personalized therapies for prostate cancer.
 Specific Aims: 1. Develop PDXs that reflect the lethal form of prostate cancer. 2. Develop a responder ID profile hypothesis according to the treatment responsiveness of fully characterized prostate cancer PDXs. 3. Validate the responder ID profile hypothesis in a clinical trial.
 Role: Co-Investigator

P50 CA140388-06A1
Title: (Logothetis and Thompson)
MD Anderson Cancer Center Prostate Cancer SPORE
Core 1: Biostatistics and Bioinformatics
 Time Commitment: 1.62 calendar
 Supporting Agency: NIH/NCI
 Grants Officer: Martinson Owusu, Phone: 240-276-6297, owusumo@mail.nih.gov
 Performance Period: 09/01/2016-08/31/2021
 Level of Funding:
 Project Goals: To provide comprehensive biostatistic and bioinformatic expertise to ensure statistical integrity and optimize data analysis for the studies in the Prostate SPORE.
 Specific Aims: 1. Provide guidance in the design and conduct of clinical trials and other experiments (including high-dimensional genomic and proteomic studies) that arise from the ongoing research of the SPORE. 2. Provide innovative and tailored statistical modeling, simulation techniques, and data analyses as needed for the main projects, developmental research and career development projects, and other cores to achieve their specific aims. 3. Ensure that the results of all projects are based on well-designed experiments and are appropriately interpreted. 4. Provide guidance in the design and use of an information system to store appropriate data generated by all projects; develop integrated computational libraries and tools for producing documented, reproducible statistical and bioinformatics analyses; and support the use of these tools for analyses conducted by and on behalf of the projects.
 Role: Co-Director

OVERLAP: None

UNIVERSITY OF MICHIGAN KEY PERSONNEL

CHINNAIYAN, Arul M.

CURRENT

UMI HG006508

Title:

(Chinnaiyan, Pienta, and Robert)

Exploring Precision Cancer Medicine for Sarcoma and Rare Cancers

Time Commitment:	10% effort, 1.20 calendar
Supporting Agency:	NIH
Grants Officer:	Zephaun Harvey, Phone: 301-435-7859, harveyz@mail.nih.gov
Performance Period:	07/19/2013-05/31/2018 (NCE)
Level of Funding:	
Project Goals:	The overall goal of this project is to bring together expertise at the University of Michigan including clinical oncology, cancer genetics, genomic science/bioinformatics, clinical pathology, social and behavioral sciences, and bioethics in order to implement clinical cancer sequencing of patients with sarcomas and other rare cancers to enable the detection of clinically significant molecular lesions (point mutations, insertions/deletions, gene fusions and rearrangements, outlier expressed genes, and amplifications/deletions).
Specific Aims:	<i>Project 1: Clinical Genomic Study.</i> 1. Accrue 500 patients with advanced or refractory rare cancer for participation in an integrated approach to Clinical Genomics; 2. Interpret results through a multi-disciplinary Sequencing Tumor Board and disclose results to patients and their physicians; 3. Measure the influence of sequence results provided to patients; 4. Determine the frequency of clinically significant germline mutations in patients undergoing comprehensive tumor sequence analysis. <i>Project 2: Sequencing, Analysis, and Interpretation of Sequencing Data;</i> 1. Process and track specimens and ensure quality control; 2. Sequence tumor and germline biospecimens; 3. Analyze sequencing data to identify clinically significant variants; 4. Interpret and translate sequence variants into clinical oncology setting; 5. Assess and evaluate costs associated with clinical sequencing.

W81XWH-12-1-0080
Title:

(Chinnaiyan)
Advancing Our Understanding of the Etiologies and Mutational Landscapes of Basal-Like, Luminal A, and Luminal B Breast Cancers

Time Commitment:	7.50% effort, 0.90 calendar
Supporting Agency:	DOD – Collaborative Innovators Award
Grants Officer:	Cheryl A. Lowery, Phone: 301-619-7150, Cheryl.Lowery@us.army.mil
Performance Period:	09/15/2012-09/14/2018 (NCE)
Level of Funding:	
Project Goals:	Sequencing of the samples to find mutations; correlate with clinical pathologic and epidemiologic factors.
Specific Aims:	1. Identify and quantify risk factors for each of the most common molecular subtypes of breast cancer, basal-like, luminal A, and luminal B tumors, in a large-scale population-based study. 2. Discover and validate the mutational landscape of basal-like, luminal A, and luminal B tumors. 3. Characterize the relationships between subtype specific risk factors and mutational signatures. 4. Develop and validate risk prediction models unique to each breast cancer subtype incorporating clinical, epidemiologic and mutation data. 5. Identify and quantify the relationships between various exposures and mutational changes on risk

of breast cancer recurrence and survival among patients with basal-like, luminal A, and luminal B tumors.

R01 CA200660

Title:

(Grembecka, Chinnaiyan)

Targeting the MLL complex in Castration Resistant Prostate Cancer

Time Commitment:

10% effort, 1.20 calendar

Supporting Agency:

NIH

Grants Officer:

Elesinmogun, Funmi, elesinmf@mail.nih.gov

Performance Period:

08/01/2016-07/31/2021

Level of Funding:

Project Goals:

To develop new therapy for castration resistant prostate cancer patients by blocking the menin-MLL interaction.

Specific Aims:

1. Develop highly potent small molecule inhibitors of the menin-MLL interaction with significantly improved potency in prostate cancer models and optimal in vivo properties. 2. We propose to study the mechanism of pharmacologic inhibition of the MLL complex in prostate cancer cells. 3. We will assess the in vivo efficacy of the menin-MLL inhibitors in mice models of prostate cancer and investigate the mechanism of resistance of response to these compounds in prostate cancer models. Upon successful completion of this project we expect to identify promising candidate compound(s) that could be further developed for clinical use to treat metastatic CRPC.

U01 CA214170

Title:

(Chinnaiyan, Tomlins)

The Early Detection Research Network: Biomarker Development Laboratories (U01): *Discovery and qualification of transcriptomic biomarkers for the early detection of aggressive prostate cancer*

Time Commitment:

15% effort, 1.80 calendar

Supporting Agency:

NIH/NCI

Grants Officer:

Peter Wirth, pw2q@nih.gov

Performance Period:

09/15/2016-08/31/2021

Level of Funding:

Project Goals/Aims:

1. Identify and develop assays to study novel aggressive prostate cancer-associated transcriptomic alterations from our MiTranscriptome analysis. 2. Characterize transcripts from Aim 1 as tissue based aggressive prostate cancer biomarkers using individual in situ hybridization assays and a multiplexed next generation sequencing (NGS). 3. Characterize transcripts from Aim 1 as non-invasive, urine-based aggressive prostate cancer early detection biomarkers through collaboration with our industry partner and multiplexed NGS.

U24 CA210967

Title:

(Nesvishkii and Chinnaiyan)

University of Michigan Proteogenomics Data Analysis Center

Time Commitment:

8% effort, 0.96 calendar

Supporting Agency:

NIH

Grants Officer:

Rodriguez, Henry, rodriguezh@mail.nih.gov

Performance Period:

09/15/2016-08/31/2021

Level of Funding:

Project Goals: To perform integrative analysis of data generated using the Clinical Proteomic Tumor Analysis Consortium (CPTAC). The proposed Center at the University of Michigan will be one of the four Centers funded by CPTAC. It will work, in coordination with other Centers, to analyze and integrate proteomics, genomics, and transcriptomics data generated for 3-4 cancer patient cohorts, ~ 100 samples in each cohort. The Center will generate data analysis reports to be shared with other members of the Consortium.

Specific Aims: 1. Assemble a comprehensive proteogenomics data analysis pipeline enabling application of two complementary strategies: (a) using mass spectrometry-based (MS) proteomics data for protein-level “validation” (and thus prioritization) of novel and aberrant cancer-specific transcripts (including alternative splice forms, mutations, etc.) identified from genomics and transcriptomic data. 2. Apply our computational pipelines to CPTAC-wide data, with a focus on presenting the results to the cancer research community in an easily accessible, highly visual form. 3. UM-PGDAC will engage, in coordination with other CPTAC centers, in a second round of prioritization work to select candidate cancer-specific proteins and peptides for subsequent targeted validation using multiplex proteomic assays.

W81XWH-14-1-0555
Title:

(Chinnaiyan, Navone)
Development of Personalized Cancer Therapy for Men with Advanced Prostate Cancer

Time Commitment:

5% effort, 0.60 calendar

Supporting Agency:

DOD

Grants Officer:

Peggie Lesnow, Phone: 301-619-2367, margaret.a.lesnow.civ@mail.mil

Performance Period:

09/22/2014-09/21/2018 (NCE – PENDING)

Level of Funding:

Project Goals:

To develop a strategy for identifying molecular therapeutic response markers of advanced prostate cancer to specific therapies by using patient-derived xenografts (PDXs) from patients with prostate cancer.

Specific Aims:

1. Develop PDXs that reflect the lethal form of prostate cancer; 2. develop a responder ID profile hypothesis according to the treatment responsiveness of fully characterized prostate cancer PDXs, and 3. validate the responder ID profile hypothesis in a clinical trial.

U01 HL126499
Title:

(Tewari)
Reference Profiles of ExRNA in Biofluids from Well-Defined Human Cohorts

Time Commitment:

4% effort, 0.48 calendar

Supporting Agency:

NIH/NHLBI

Grants Officer:

Tracee Foster, Phone: 301-402-3843, gilchrit@mail.nih.gov

Performance Period:

08/01/2014-04/30/2019

Level of Funding:

Project Goals:

To generate quality-controlled, comprehensive RNA sequencing-based profiles of human body fluids including plasma, serum and urine from healthy individuals.

Specific Aims: 1. Sequence exRNAs present in biofluids of healthy individuals. 2. Identify and annotate both endogenously and exogenously-derived exRNA sequences. 3. Perform validation and absolute quantification of exRNAs using droplet digital PCR (ddPCR). 4. Perform cross-validation service and integrate scientifically with other Consortium teams.

Role: Co-Investigator

P50 CA186786

Title: (Chinnaiyan) SPORE in Prostate Cancer

Project 1: A Precision Medicine Approach to Elucidate Mechanisms of Progression and Resistance to Therapy in Advanced Prostate Cancer.

Project 4: Development of lncRNAs as Prostate Cancer Biomarkers in Urine

Core 3: Tissue Core

Time Commitment: 20% effort, 2.40 calendar

Supporting Agency: NIH/NCI

Grants Officer: Andrew Hruszkewycz, Phone: 301-496-8528, hruszkea@mail.nih.gov

Performance Period: 09/11/2014-08/31/2019

Level of Funding:

Project Goals: The overall goal of this grant is the development of new approaches to the prevention, early detection, diagnosis and treatment of prostate cancer through translational research.

Specific Aims: *Project 1 Aims:* 1. Discovery and nomination of novel molecular subtypes of prostate cancer; 2. Characterize associations of molecular subtypes of prostate cancer with clinical outcome and/or aggressiveness of disease in a radical prostatectomy cohort; 3. Characterize associations of molecular sub-types of prostate cancer with clinical outcome.

Project 4 Aims: 1. Employ a compendium of prostate cancer RNA-Seq data to nominate lncRNAs for assessment in urine. 2. Develop a urine multiplex panel of lncRNAs (including PCAS and Schalpl) that, when combined with TMPRSS2-ERG, will identify men who are more likely to have prostate cancer and ultimately to prevent unnecessary prostate biopsies in men with a low likelihood of cancer. 3. Define a panel of lncRNAs in urine for the detection of high grade prostate cancer. In this Aim, we will identify individual lncRNAs or combinations with PGAS+TMPRSS2-ERG that assist in non-invasively detecting high grade prostate cancer in urine.

Core 3 aims: 1. Protect patient welfare; 2. Acquisition and processing of prostate tissues for research; 3. Maintenance of clinical and pathology data with links to molecular studies; 4. Provide high quality pathologic review of prostate tissues; 5. Provide expert pathology consultation; 6. Perform quality assessment of prostate tissues and clinical data; 7. Develop technology appropriate for pathology-based translational research.

Roles: Overall Program Director, Co-Leader of Projects 1 and 4; Director of Core 1 (Administration) and Co-Core Director of Core 3 (Tissue Core)

OVERLAP: None

ROBINSON, Dan

CURRENT

W81XWH-12-1-0080

Title:

(Chinnaiyan)

Advancing Our Understanding of the Etiologies and Mutational Landscapes of Basal-Like, Luminal A, and Luminal B Breast Cancers

Time Commitment:

10% effort, 1.20 calendar

Supporting Agency:

DOD – Collaborative Innovators Award

Grants Officer:

Cheryl A. Lowery, Phone: 301-619-7150, Cheryl.Lowery@us.army.mil

Performance Period:

09/15/2012-09/14/2018 (NCE)

Level of Funding:

Project Goals:

Sequencing of the samples to find mutations; correlate with clinical pathologic and epidemiologic factors.

Specific Aims:

1. Identify and quantify risk factors for each of the most common molecular subtypes of breast cancer, basal-like, luminal A, and luminal B tumors, in a large-scale population-based study. 2. Discover and validate the mutational landscape of basal-like, luminal A, and luminal B tumors. 3. Characterize the relationships between subtype specific risk factors and mutational signatures. 4. Develop and validate risk prediction models unique to each breast cancer subtype incorporating clinical, epidemiologic and mutation data. 5. Identify and quantify the relationships between various exposures and mutational changes on risk of breast cancer recurrence and survival among patients with basal-like, luminal A, and luminal B tumors.

Role:

Co-Investigator

W81XWH-14-1-0555

Title:

(Chinnaiyan, Navone)

Development of Personalized Cancer Therapy for Men with Advanced Prostate Cancer

Time Commitment:

16% effort, 1.92 calendar

Supporting Agency:

DOD

Grants Officer:

Peggie Lesnow, Phone: 301-619-2367, margaret.a.lesnow.civ@mail.mil

Performance Period:

09/22/2014-09/21/2018 (NCE – PENDING)

Level of Funding:

Project Goals:

To develop a strategy for identifying molecular therapeutic response markers of advanced prostate cancer to specific therapies by using patient-derived xenografts (PDXs) from patients with prostate cancer.

Specific Aims:

1. Develop PDXs that reflect the lethal form of prostate cancer; 2. Develop a responder ID profile hypothesis according to the treatment responsiveness of fully characterized prostate cancer PDXs; 3. Validate the responder ID profile hypothesis in a clinical trial.

Role:

Co-Investigator

P50 CA186786

Title:

(Chinnaiyan)

SPORE in Prostate Cancer, Project 1: A Precision Medicine Approach to Elucidate Mechanisms of Progression and Resistance to Therapy in Advanced Prostate Cancer

Time Commitment:

16% effort, 1.92 calendar

Supporting Agency:

NIH/NCI

Grants Officer:	Andrew Hruszkewycz, Phone: 301-496-8528, hruszkea@mail.nih.gov
Performance Period:	09/11/2014-08/31/2019
Level of Funding:	
Project Goals:	Discovery and nomination of novel molecular sub-types of prostate cancer; 2. Characterize associations of molecular sub-types of prostate cancer with clinical outcome and/or aggressiveness of disease in a radical prostatectomy cohort; 3. Characterize associations of molecular sub-types of prostate cancer with clinical outcome
Specific Aims:	Same as above.
Role:	Co-Investigator

OVERLAP: None

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CURRENT

W81XWH-14-1-0555	(Chinnaiyan)
Title:	Development of Personalized Cancer Therapy for Men with Advanced Prostate Cancer
Time Commitments:	30.00% effort, 3.60 calendar
Supporting Agency:	DOD
Grants Officer:	Peggie Lesnow, Phone: 301-619-2367, margaret.a.lesnow.civ@mail.mil
Performance Period:	09/22/2014-09/21/2018 NCE
Level of Funding:	To develop a strategy for identifying molecular therapeutic response markers of advanced prostate cancer to specific therapies by using patient-derived xenografts (PDXs) from patients with prostate cancer.
Project Goals:	
Specific Aims:	1. Develop PDXs that reflect the lethal form of prostate cancer; 2. Develop a responder ID profile hypothesis according to the treatment responsiveness of fully characterized prostate cancer PDXs; 3. Validate the responder ID profile hypothesis in a clinical trial.
Role:	Co-Investigator

5 P50 CA186786	(Chinnaiyan)
Title:	SPORE in Prostate Cancer, Project 1: A Precision Medicine Approach to Elucidate Mechanisms of Progression and Resistance to Therapy in Advanced Prostate Cancer
Time Commitments:	10% effort, 1.20 calendar
Supporting Agency:	NIH/NCI
Grants Officer:	Andrew Hruszkewycz, Phone: 301-496-8528, hruszkea@mail.nih.gov
Performance Period:	09/11/2014-08/31/2019
Level of Funding:	
Goals:	1. Discovery and nomination of novel molecular sub-types of prostate cancer; 2. Characterize associations of molecular sub-types of prostate cancer with clinical outcome and/or aggressiveness of disease in a radical prostatectomy cohort; 3. Characterize associations of molecular sub-types of prostate cancer with clinical outcome.
Specific Aims:	Same as above
Role:	Research Investigator

OVERLAP: None

What other organizations were involved as partners?

The Partnering PI, Dr. Arul Chinnaiyan, is from the University of Michigan. Drs. Chinnaiyan and Navone as well as the University of Michigan and MD Anderson teams worked closely to design and interpret the studies performed during the period of this progress report. Partnering PI performed all next generation sequencing studies and also made available the results in a timely manner as well as the software and knowledge necessary to the interpretation of next generation sequencing results by the MD Anderson team.

Partnering PI Location: The University of Michigan
400 E. Medical Center Drive
5316 CCC
Ann Arbor, MI 48109-5940

SPECIAL REPORTING REQUIREMENTS

Not Applicable

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.