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

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RECIPIENT: The University of Texas
Houston, TX 77030

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14. ABSTRACT

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) that are responders and nonresponders (primary and secondary resistance) to therapies that had demonstrated clinical activity. We will identify genomic alterations via integrative genomic analysis of these PDXs. The MD Anderson and Michigan Center for Translational Pathology teams will interact closely to analyze integrative genomic analysis results to generate a responder ID profile hypothesis. The validity of the responder ID profiles will be assessed in clinical trials. We had already identified prostate cancer PDXs responders and non-responders to a therapy that targets fibroblast growth factor receptors pathway. We are now generating tissue samples to perform integrative genomic analysis.

15. SUBJECT TERMS
Bone metastases, targeted therapy, prostate cancer

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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) that are responders and nonresponders (primary and secondary resistance) to therapies that had demonstrated clinical activity. We will identify genomic alterations via integrative genomic analysis of these PDXs. The MD Anderson and the Michigan Center for Translational Pathology (MCTP) teams will interact closely to analyze integrative 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. 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 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, Robinson, and 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, Araujo, 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, 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, Troncoso, Broom, and Drs. Chinnaiyan, Robinson, and Wu)**

- Abiraterone and enzalutamide clinical study (NCT01650194; PI, C. J. 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. We have established new PDXs derived from the prostate and bone metastases. Table 1 outlines the lines established and the current passage number (MD Anderson site – Dr. Navone's Laboratory).

The specific objective was to have a panel of PDXs that would reflect human prostate cancer so that they can be utilized for our preclinical studies. We continue to develop PDXs with about 40% success rate and they maintain the fidelity of the human tumor of origin. These PDXs will also make available to the scientific community through a material transfer agreement.

Table 1. **Prostate Cancer Tissue Specimens Processed for PDX Development and PDX Developed between 1/1/2013 and 4/20/2015**

Date	Patient Number	Human donor tumor information					PDX name (MDA PCa)	PDX information
		Procedure type	Pathology diagnosis	Anatomic description	Prior therapy	Tumor site		Current passage
1/13	259	Radical prostatectomy	Adenocarcinoma	Local extension	No prior therapy	Right base	259-9	5
						Right lobe peripheral zone	259-11	3
2/13	261	Transurethral resection of the prostate	Metastatic Adeno carcinoma	Metastatic	Androgen ablation and chemotherapy	Prostate	261	3
4/13	265	cystoprostatectomy	Metastatic carcinoma with neuro endocrine differentiation	Metastatic	Androgen ablation and chemotherapy	Left trigono	265-6	4
8/13	267	Radical prostatectomy	Metastatic Adeno carcinoma	Metastatic	Androgen ablation	Left lobe peripheral zone	267-9	2
9/13	268	Radical prostatectomy	Metastatic Adeno carcinoma	Metastatic	no prior therapy	Left lobe peripheral zone	268-12	3

Date	Patient Number	Human donor tumor information					PDX name (MDA PCa)	PDX information
		Procedure type	Pathology diagnosis	Anatomic description	Prior therapy	Tumor site		Current passage
9/13	269	Radical prostatectomy	Adeno carcinoma	Local extension	Androgen ablation	Right lobe peripheral zone	269-9	6
9/13	270	Bone marrow biopsy	Metastatic carcinoma	Metastatic	Androgen ablation	Bone marrow	270	6
9/13	271	Radical prostatectomy	Adeno carcinoma	Local extension	Androgen ablation	Right lobe peripheral zone	271-9	5
10/13	272	Radical prostatectomy	Adeno carcinoma	Local extension	No prior therapy	Right lobe peripheral zone	272-9	4
11/13	274	Biopsy	Metastatic Adeno carcinoma	Metastatic	Androgen ablation and chemotherapy	Bone	274-2	2
3/14	279	Radical prostatectomy	Metastatic Adeno carcinoma	Metastatic	Androgen ablation and chemotherapy	Left lobe peripheral zone	279-10	4
9/14	285	Transureteral resection of bladder tumor	Carcinoma	Local extension	Androgen ablation	Bladder trigono	285-1	2
						Bladder trigono	285-3	1
9/14	286	Biopsy	Metastatic carcinoma	Metastatic	No prior therapy	Bone marrow	286	1
10/14	287	Transurethral resection of the prostate	Adenocarcinoma	Local extension	Androgen ablation	Prostatic urethra	287-A	1
						Prostatic urethra	287-B1	1
10/14	291	Radical prostatectomy	Metastatic Adeno carcinoma	Metastatic	Androgen ablation	Right prostate	291-11	1
10/14	292	Radical prostatectomy	No tumor remaining after therapy	Prostate	Androgen ablation	Left prostate	292-1	2
						Left lobe peripheral zone	292-3	2
						Right prostate	292-5	2
11/14	293	Radical prostatectomy	Metastatic Adeno carcinoma	Metastatic	Androgen ablation and chemotherapy	Right lobe peripheral zone	293-9	1
						Left lobe peripheral zone	293-12	1
11/14	295	Prostatectomy	Metastatic Adenocarcinoma	Metastatic	Androgen ablation and radiotherapy	Left lobe peripheral zone	295-10	1
						Left lobe peripheral zone	295-12	1
						Midpostmid line	295-14	1
						Left lobe peripheral zone	295-16	1
2/15	298	Bone marrow biopsy	Metastatic Carcinoma	Metastatic		Bone marrow	298-1	1
4/15	306	Radical prostatectomy	Adeno carcinoma	Prostate		Left prostate	306-11	1
						Right prostate	306-14	1

*In addition to these lines, there are 25 that were implanted between 3/26/2015 and 10/2/2015 but have not been passaged yet.

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.

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).

We tested in prostate cell lines LNCap and VCap. We are in the process of identifying prostate cancer PDX responders and not responders to cabozantinib (University of Michigan, Dr. Chinnaiyan Lab).

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 Lab).

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, 9/2014. 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.

For this testing 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. Briefly, a preclinical study using cells derived

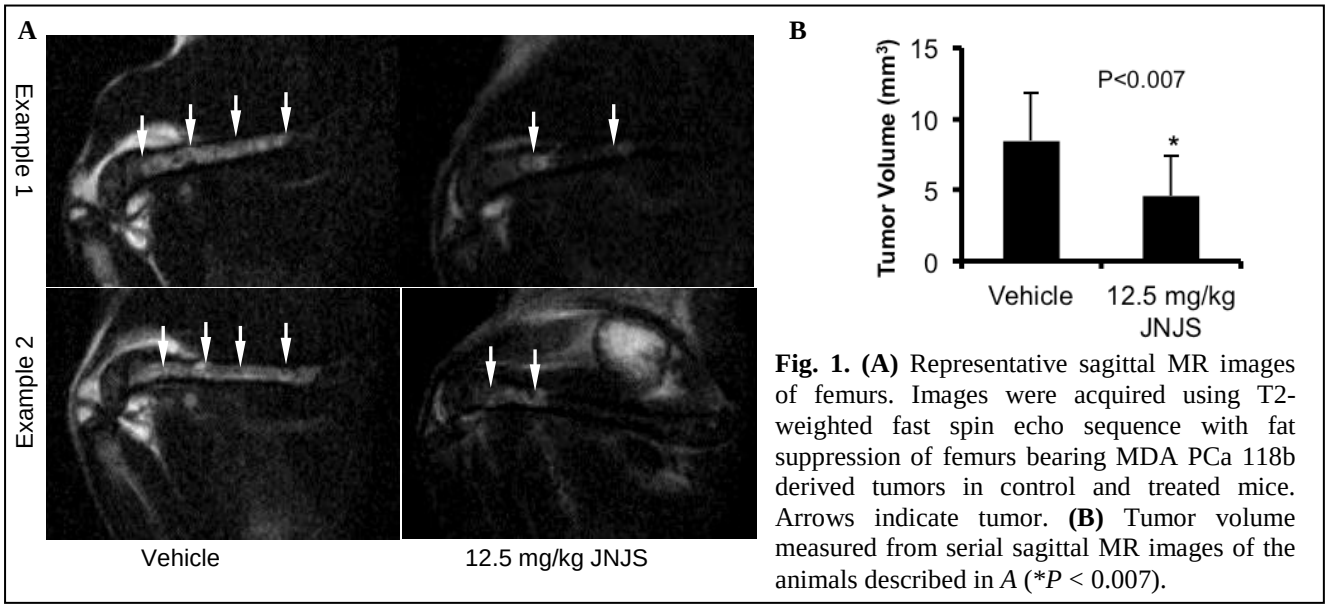


Fig. 1. (A) Representative sagittal MR images of femurs. Images were acquired using T2-weighted fast spin echo sequence with fat suppression of femurs bearing MDA PCa 118b derived tumors in control and treated mice. Arrows indicate tumor. **(B)** Tumor volume measured from serial sagittal MR images of the animals described in *A* (*$P < 0.007$).

from MDA PCa 118b PDX growing in the bone of male SCID mice and treated with NVP-BGJ398 and JNJS 42756493 indicated minimal antitumor effect of NVP-BGJ398 and potent antitumor effect of JNJS 42756493. We outline here results of the studies performed with JNJS 42756493. We used 1 control group (n=10) (vehicle 10ml/kg x BID) and a treatment group (n=13) (JNJS 10ml/kg x BID) according to Janssen Pharmaceutical instructions. Treatment started 10 days after cell injection. After 3 weeks of treatment, we performed MRI analyses of control and treatment groups to assess tumor volume. Fig. 1 outlines the results of MRI analyses indicating that JNJS is active in controlling the growth of prostate cancer cells in bone. After MRI was performed, mice were killed and tumor-bearing femurs were dissected out and formalin fixes, paraffin embedded (n=5) to perform histopathological studies or flash frozen (n=5) for molecular studies. At the time of processing and in alignment with our MRI results we noticed that, macroscopically the femurs of the treated mice were thinner (data not shown).

We subsequently performed Immuno-histochemical analysis of FGFR1 expression in MDA PCa 118b growing in the bone of mice in the vehicle and JNJS treated mice. We observed a reduction of FGFR1 expression in tumors of the treated group compared with vehicle treated group (Fig. 2). However, since immunohistochemistry is not a quantitative method, we will assess FGFR1 expression by western blot analyses and RT-PCR to gain more confidence in these results. We will subsequently assess other immunohistopathological parameters (e.g., proliferation, apoptosis), of known candidate markers regulated by FGFR signaling (i.e., p-FRS2, p-ERK1/2, p-S6k).

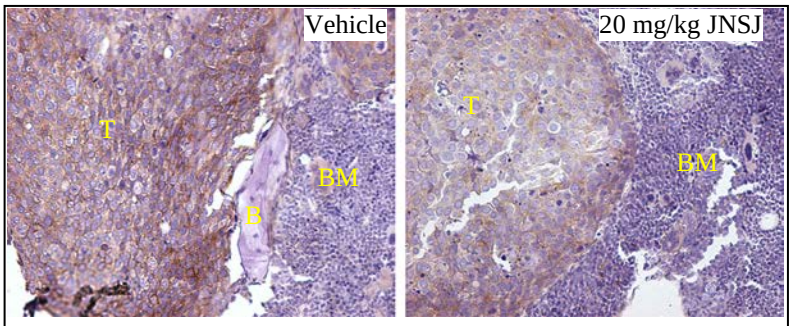


Fig. 2. Immunohistochemical analysis of FGFR1 expression in MDA PCa 118b PDXs growing in the bone of male SCID mice. T: tumor: B: bone: BM bone marrow

We had initiated a second preclinical study treating MDA PCa 118b growing in the bone of mice with JNJS 42756493. This study will set aside tissue samples for comprehensive genomic analyses and will also develop resistant lines.

Due to dovitinib withdraw by Novartis; we had to spent significant amount of time to identify other tyrosine kinase FGFR inhibitors. As a result we had a delay in the initiation of our studies and a positive balance in our budget that we request to carry forward to next budget period.

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

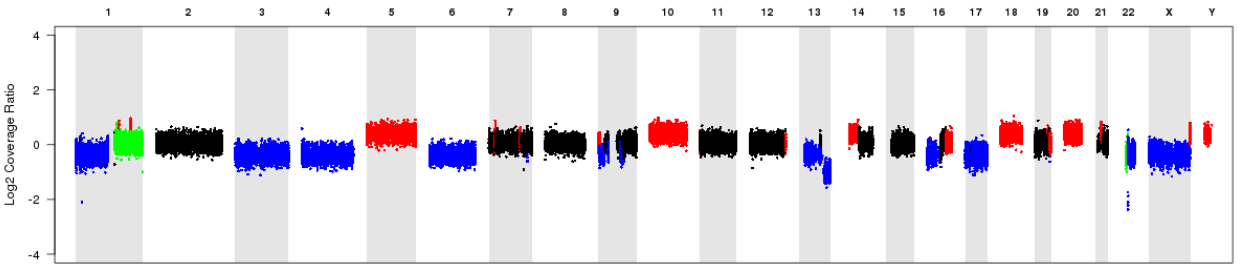
Subtask 1: We have sequenced the transcriptomes and analyzed the baseline expression and fusion status for 23 PDX prostate cancer lines developed at MD Anderson. Fusion analysis of the first 19 cases demonstrates 10 cases are ETS fusion positive, while 9 cases are ETS fusion negative. Notably, this distribution of ETS fusion status mirrors the distribution of ETS fusions in prostate cancer in general. The exomes of 2 pretreatment PDX models and matched normals have been sequenced and analyses of copy number aberrations, somatic SNVs and indels are underway. Four additional

pretreatment PDX xenograft models have been sequenced for whole exome without matched normals. All library preparation and sequencing performed to date have passed the same quality control standards as established in our CLIA certified clinical sequencing lab.

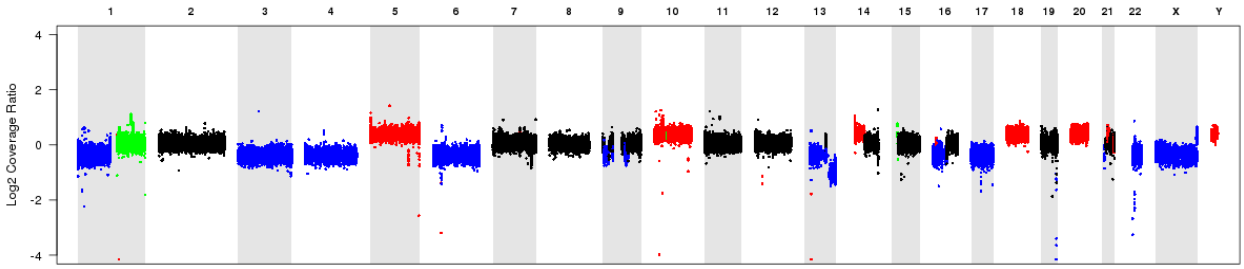
Gene	Somatic Mutation	Somatic Evidence	Germline Variant	Copy Number Status	Fusion Status	Expression (FPKM)
TP53	NM_000546, p.Y234H	50/96 (52%) in Tumor	None Detected	Copy neutral LOH	None Detected	112.5
NOTCH2	NM_024408 ,p.Q2360X	899/1075 (84%) in Tumor	None Detected	Gain (9 copies)	None Detected	124.3
WNT3A	NM_033131, p.R192C	20/127 (16%) in Tumor	None Detected	Gain (5 copies)	None Detected	0
RYR2	NM_001035, p.E4137K	247/940 (26%) in Tumor	None Detected	Gain (5 copies)	None Detected	0
TCF7L2	NM_030756, p.Q373E	65/251 (26%) in Tumor	None Detected	No copy number change	None Detected	26.4
MAP3K12	NM_001193511, p.D30E	43/164 (26%) in Tumor	None Detected	No copy number change	None Detected	2.3
ELK3	NM_005230, p.S211P	95/354 (27%) in Tumor	None Detected	No copy number change	None Detected	5.1
SOX1	NM_005986, p.V161M	7/55 (13%) in Tumor	None Detected	No copy number change	None Detected	0
TAOK2	NM_016151, p.V835I	99/245 (40%) in Tumor	None Detected	No copy number change	None Detected	15.4
NLRP1	NM_001033053, p.A1229S	66/225 (29%) in Tumor	None Detected	Copy neutral LOH	None Detected	0.6
HDAC5	NM_001015053, p.P830S	16/59 (27%) in Tumor	None Detected	No copy number change	None Detected	21.6
TCF4	NM_001083962, p.R401Q	69/231 (30%) in Tumor	None Detected	No copy number change	None Detected	1.7
CYP4F2	NM_001082, p.T472M	7/42 (17%) in Tumor	None Detected	Gain (4 copies)	None Detected	1.3
SLC19A1	NM_194255, p.R465Q	41/243 (17%) in Tumor	None Detected	Gain (3 copies)	None Detected	53
ODC1	None Detected	None Detected	NM_002539, p.G84R	Gain (3 copies)	None Detected	39.1
HOXD4	None Detected	None Detected	NM_014621, p.P53S	No copy number change	None Detected	0
PMS1	None Detected	None Detected	NM_000534, p.T75I	No copy number change	None Detected	11.7
FANCC	None Detected	None Detected	NM_000136, p.Q465R	Copy neutral LOH	None Detected	6.8
PALB2	None Detected	None Detected	NM_024675, p.L939W	No copy number change	None Detected	7.1
LAMC2	None Detected	None Detected	NM_005562, p.R295Q	No copy number change	None Detected	4.7
PTPRF	None Detected	None Detected	None Detected	Gain (3 copies)	PTPRF-PHGDH Fusion	249.2
ABI1	None Detected	None Detected	None Detected	Gain (9 copies)	None Detected	118.9
CACNB2	None Detected	None Detected	None Detected	Gain (7 copies)	None Detected	0.5
FUBP1	None Detected	None Detected	None Detected	Gain (8 copies)	None Detected	97.6
HSD3B1	None Detected	None Detected	None Detected	Gain (9 copies)	None Detected	0.1
MLLT10	None Detected	None Detected	None Detected	Gain (7 copies)	None Detected	55.3
MSH4	None Detected	None Detected	None Detected	Gain (8 copies)	None Detected	0.3
NF1	None Detected	None Detected	None Detected	Gain (20 copies)	None Detected	12.2
SUV39H2	None Detected	None Detected	None Detected	Gain (10 copies)	None Detected	35.7
PHGDH	None Detected	None Detected	None Detected	No copy number change	PTPRF-PHGDH Fusion	532.8

We have optimized a copy number analysis module using exome sequencing data from tumor samples and pooled normal samples that eliminates the absolute requirement for matched normal for accurate copy number assessment shown below.

Tumor vs. Matched Normal



Tumor vs. Pooled Normal



Additionally, we have developed a RNA-SEQ approach for sensitive fusion detection in a wide range of RNAs from various sample types and RNA quality. (Cieslik et al. "The use of exome capture RNA-seq for highly degraded RNA with application to clinical cancer sequencing." Genome Research, Sept. 2015) Completion of an analysis pipeline that detects genomic structural rearrangements using chimeric read information from RNA-SEQ data is nearing completion. In summary the necessary analysis tools are in place to detect a range of aberrations which might generate resistance in our upcoming sample sets.

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

Nothing to Report

How were the results disseminated to communities of interest?

Nothing to Report

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

During the next period Dr. Navone will develop JNJS 42756493 resistant PDXs and will 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.

We will Identify prostate cancer PDX responders and nonresponders (primary resistance) to cabozatinib, abiraterone plus enzalutamide and establish lines of PDXs resistant (acquired resistance).

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

Nothing to Report

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

Due to dovitinib withdraw by Novartis we had to spend significant amount of time to identify other tyrosine kinase FGFR inhibitors. As a result, we had a delay in the initiation of our studies and a positive balance in our budget that we request to carry forward to next budget period. We will compensate this delay in the coming year.

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

Nothing to report

Significant changes in use or care of human subjects

Nothing to report

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

Nothing to report

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 month

Contribution to Project:	Dr. Araujo provides clinical-related 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 month
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:	**Xinhai Wan**
Project Role:	Collaborator
Nearest person month worked:	4.80 calendar month
Contribution to Project:	Dr. Wan is responsible for intrabone injection of prostate cancer cells in mice and the in vivo experiments involving laboratory animals. He performs the immunohistochemical studies of tissue samples and the molecular and cell biology studies related to the in vivo studies. In addition, he communicates with oncologists and pathologists to collect the information and discuss the interpretation of the results.
Funding Support:	Funding support is provided from this award.

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
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
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
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:	6.0 calendar
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:	1.20 calendar
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. Please note that Dr. Nallasivam Palanisamy left the University of Michigan.

MD Anderson Key Personnel

NAVONE, Nora
ACTIVE

Movember Action Plan	**(Navone)**
Title:	**Initiative: GAP1 Xenograft Project Integration Plan** **Development of Prostate Cancer Xenografts to Model Human Prostate Cancer**
Time Commitment:	1% effort, 0.12 calendar
Supporting Agency:	Prostate Cancer Foundation-Movember Action Plan Initiative
Grants Officer:	Dr. Mark Buzza, Movember Foundation

	1250 Fourth Street, Santa Monica CA 90401 Phone: 301-570-4700
Performance Period:	01/01/2014-12/31/2015
Level of Funding:	$70,068 annual direct
Project Goals:	To create a catalog of prostate cancer patient-derived xenografts developed in different institutions around the world. This catalog would contain basic information of the prostate cancer patient-derived xenografts associated to expression of genes most frequently altered in prostate cancer as assessed by immunohistochemical analyses of tissue microarrays.
Specific Aims:	Not Applicable.

SINF	**(Navone)**
Title:	**Modeling Prostate Cancer Bone Metastasis in the Mouse-basic Biology and Translational Impact**
Time Commitment:	10% effort, 1.20 calendar (unsalaried)
Supporting Agency:	MD Anderson Cancer Center – Sister Institution Network Fund
Grants Officer:	Govind Narasimhan, Director, Research Finance Phone: 713-792-4706 gnarasim@mdanderson.org
Performance Period:	11/01/2013-11/30/2016 NCE
Level of Funding:	$50,000 annual direct
Project Goals:	The ultimate goal is to not only have a more in-depth understanding of the signaling circuitry that drives osteoblastic bone metastasis in CRPC patients, but to also provide a rational basis for the use of FGFR-targeted agents and a model system for anticipated resistance mechanisms.
Specific Aims:	1) To assess the effects of FGFR-targeted therapies on osteoblastic prostate cancer bone metastases in a patient-derived xenograft mouse model. 2) To characterize the response to FGFR-targeted therapies with a focus on chromosomal instability. 3) To analyze potential genetic and functional resistance mechanisms to FGFR-targeted therapies in the mouse model and in paired patient biopsy samples.

Prime: PR110555 (Wang); CPRIT Subaward: S110092

Title:	**Activation of Prostate Cancer Stem Cells through Aberrant FGF Signaling**
Time Commitment:	10% effort, 1.20 calendar
Supporting Agency:	CPRIT – The Texas A & M Research Foundation
Grants Officer:	Jane Zuber, Director, Contracts & Grants, Texas A&M Univ. System 400 Harvey Mitchell Pkwy South, Suite 300 College Station, TX 77845-4321 Phone: 979-845-8615 jzuber@tamus.edu
Performance Period:	07/01/2011-06/30/2016
Level of Funding:	$120,000 annual direct

Project Goals:	The overall goal is to study whether bidirectional FGF signaling between P-CSCs and the stromal compartment favors prostate cancer progression in bone.
Specific Aims:	1) To investigate the molecular mechanism by which aberrant FGF signaling promotes P-CSC survival and self-renewal. 2) To study whether bidirectional FGF signaling between P-CSCs and the stromal compartment favors prostate cancer progression in bone.
Role:	Subcontract PI

W81XWH-14-1-0554	**(Navone)**
Title:	**Development of Personalized Cancer Therapy for Men with Advanced Prostate Cancer**
Time Commitment:	15% effort, 1.80 calendar
Supporting Agency:	DOD
Grants Officer:	Janet P. Kuhns, Contracting Officer Phone: 301-619-2827 janet.p.kuhns.civ@mail.mil
Performance Period:	09/22/2014-09/21/2017
Level of Funding:	$125,000 annual direct
Project 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.

Janssen	**(Navone)**
Title:	**FGFR Inhibitors in Prostate Cancer Bone Metastasis**
Time Commitment:	15% effort, 1.80 calendar
Supporting Agency:	Janssen Research and Development
Grants Officers:	James Bischoff, Sr. Dir., Phone: 215-628-5971, jbischol@its.jnj.com Jhilik De, Administrative Contact, Jde5@its.jnj.com
Performance Period:	08/14/2014-07/31/2017
Level of Funding:	$115,270 annual direct
Project Goals:	This program's goal is to test the antitumor efficacy of a pan-FGFR inhibitor (JNJS 42756493) 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.

ARAUJO, John

None

BROOM, Bradley

ACTIVE

Bioinformatics Gift	**(Weinstein)**
Title:	**MD Anderson Cancer Center Bioinformatics Gift**
Time Commitment:	15.08% effort, 1.81 calendar
Supporting Agency:	Michael and Susan Dell Foundation
Grants Officer:	Claudia Delgado, Executive Director, Grants and Contracts awardnotice@mdanderson.org
Performance Period:	04/25/2011-04/04/2016
Level of Funding:	$377,733 annual direct
Project Goals:	The goal of the project is to develop methods of analysis for microarray and sequencing-based data that aid in the development of personalized therapies for cancer on the basis of molecular biomarkers and biosignatures. The projects under way are largely, but not exclusively focused on non-small cell lung cancer.
Specific Aims:	Same as above.
Role:	Co-Investigator

P30 CA016672	**(DePinho)**
Title:	**Cancer Center Support (CORE) Grant**
Time Commitment:	39% effort, 4.68 calendar
Supporting Agency:	NIH/NCI
Grants Officer:	Leslie Hickman Phone: 301-631-3009 hickmanl@mail.nih.gov
Performance Period:	09/04/1998-06/30/2016
Level of Funding:	$109,644 annual direct
Project Goals:	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.
Specific Aims:	Same as above.
Role:	Co-Investigator

5 U24 CA143883	**(Weinstein)**
Title:	**Integrative Pipeline for Analysis & Translational Application of TCGA Data (GDAC)**
Time Commitment:	14.08% effort, 1.69 calendar
Supporting Agency:	NIH/NCI
Grants Officer:	Rosermary Ward, Grants Management Specialist Phone: 240-276-6320 wardros@mail.nih.gov
Performance Period:	09/29/2009-07/31/2016
Level of Funding:	$1,525,818 annual direct

Project Goals:	The objective of this study is to perform a uniform characterization to monitor status of relevant cellular signaling in both xenograft models at their early passage stage and its corresponding donor tumor tissues.
Specific Aims:	The proposed Genome Data Analysis Center B (GDAC B) will work cooperatively with other GDACs funded by The Cancer Genome Atlas (TCGA) project to (i) develop an innovative, integrative pipeline for systems-level analysis of TCGA's molecular profiling data on many different types of human tumors and (ii) apply that pipeline and its component modules to TCGA data to address important biological and clinical questions. An overarching goal is to 'personalize' the management of patients' cancers on the basis of new tumor biomarkers and biosignatures.
Role:	Investigator
PCa Moonshot	**(Logothetis and Thompson)**
Title:	**MD Anderson Moon Shot Program** *Pilot Project 1:* Identification of differentially expressed biomarkers in biospecimens derived from men with indolent versus aggressive prostate cancer *Pilot Project 3:* Imaging local prostate cancer heterogeneity by monitoring citrate acid cycle metabolites and cholesterol precursor metabolites
Time Commitment:	10% effort, 1.20 calendar
Supporting Agency:	MD Anderson, Prostate Cancer Moon Shot
Grants Officer:	Claudia Delgado, Executive Director, Grants and Contracts awardnotice@mdanderson.org
Performance Period:	09/01/2015-08/31/2016
Level of Funding:	$1,380,374 annual direct
Project Goals:	To reduce prostate cancer mortality through intensive novel androgen signaling inhibitor-based clinical trials, unprecedented tissue resources, and the development of novel concepts for the advancement of targeted therapy-based clinical trials for treatment refractory disease.
Specific Aims:	Not applicable
Role:	Co-Investigator
W81XWH-14-1-0554	**(Navone and Chinnaiyan)**
Title:	**Development of Personalized Cancer Therapy for Men with Advanced Prostate Cancer**
Time Commitment:	1.83% effort, 0.22 calendar
Supporting Agency:	DOD-PCRP Synergistic Idea Development Award
Grants Officer:	Peggi Lesnow, Grants Specialist Phone: 301-619-2367 Margaret.a.lesnow.civ@mail.mil
Performance Period:	09/22/2014-09/21/2017
Level of Funding:	$125,000 annual direct
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

University of Michigan Key Personnel

CHINNAIYAN, Arul M.

ACTIVE

R01 CA154365	**(Beer and Chinnaiyan)**
Title:	**Identification and Characterization of Gene Fusions in Lung Adenocarcinoma**
Time Commitment:	3% effort, 0.36 calendar
Supporting Agency:	NIH/NCI
Grants Officer:	Rebecca Brightful Phone: 301-631-3011 brightfr@mail.nih.gov
Performance Period:	04/01/2011-03/31/2016
Level of Funding:	$92,500 annual direct
Project Goals:	To identify new gene-fusions in lung cancer utilizing a newly developed bioinformatics approach combined with next-generation sequencing data.
Specific Aims:	1) Functional characterization of the R3HDM2-NFE2 gene fusion in H1792 lung cancer cells, 2) Determine the frequency of occurrence in primary lung cancer and functionally characterize the novel HSPA1ANFKBIL1; 3) Functional characterization of novel gene fusions in lung cancer.

SU2C	**(Chinnaiyan)**
Title:	**Precision Therapy of Advanced Prostate Cancer**
Time Commitment:	5% effort, 0.60 calendar
Supporting Agency:	AACR-PCF-SU2C
Grants Officer:	Frederic Biemar Phone: 215-446-7261 frederic.biemar@aacr.org
Performance Period:	08/01/2012-07/31/2016 (NCTX)
Level of Funding:	$538,355 annual direct
Project Goals:	The overall goal of this proposal is to catalyze the interaction of a multi-disciplinary team of investigators, with a track record of accomplishments in prostate cancer research, to work together on the challenging problem of metastatic castration resistant prostate cancer (CRPC).

Specific Aims:	1) Establish a multi-institutional infrastructure incorporating 5 leading prostate cancer clinical sites, 2 sequencing and computational analysis sites, linked with appropriate sample and data coordination; 2) Establish a prospective cohort of 500 patients (the "CRPC 500") utilizing the multi-institutional infrastructure to support the clinical use of integrative prostate cancer sequencing, analysis, and clinical trial decision making; 3) Conduct parallel, preclinical in vivo functional studies of resistance biomarkers and of SU2C-PCF sponsored combination therapies; 4) Identify molecular determinants of abiraterone sensitivity and acquired resistance in patients; 5) Conduct clinical trials of novel combinations targeting AR and/or the PTEN pathway, based on existing preclinical data and an understanding of resistance mechanisms; 6) Identify molecular determinants of sensitivity and acquired resistance to PARP inhibitors in patients.
PCF Award	**(Chinnaiyan, Wang, Feng)**
Title:	**Therapeutic Targeting of BET Bromodomain Proteins in Castration-Resistant Prostate Cancer**
Time Commitment:	1% effort, 0.12 calendar
Supporting Agency:	Prostate Cancer Foundation
Grants Officer:	Dr. Howard Soule 1250 4th Street Santa Monica, CA 90401 applications@pcf.org
Performance Period:	10/01/2013-08/31/2016
Level of Funding:	$166,666 annual direct
Project Goals:	Determine the role of BET bromodomain proteins in prostate cancer progression and assess the use BET inhibitors in advanced prostate cancer.
Specific Aims:	1) Design and discovery of highly potent BET bromodomain small molecule inhibitors with optimized in vivo properties; 2) Interrogate the AR-BRD4 signaling axis with novel BET bromodomain inhibitors; 3) Establish the efficacy of BET bromodomain inhibition in vivo
PC121111	**(Scher)**
Title:	**Toward the Practice of Precision Medicine: Multicenter Validation of Biomarker Assays for Clinical Management of Prostate Cancer**
Time Commitment:	7.58% effort, 0.91 calendar
Supporting Agency:	DOD
Grants Officer:	Kathy E. Robinson 820 Chandler Street Fort Detrick MD 21702-5014
Performance Period:	09/30/2013-09/29/2016
Level of Funding:	$300,000 annual direct
Project Goals:	Establish and validate TMPRSS2:ERG assays; Validate the utility of the TMPRSS2:ERG TMA assay for the non-invasive detection of clinically significant prostate cancer in urine; Validate the ERG

	rearrangement FISH assay on tissues and determine the prevalence of ERG rearrangements in isolated precursor and diagnostically challenging lesions.
Specific Aims:	1) To cross-validate an initial set of assays for biomarkers corresponding to the AR and PI3K/PTEN axes ready for near-term filing with the FDA for use in prospective integral biomarker-driven trials in prostate cancer; 2) To use the centralized infrastructure of the Assay Validation Coordinating Center to cross-validate additional assays for biomarkers identified via established and emerging discovery platforms (i.e., NCI Prostate Cancer SPOREs, PCF, SU2C, and TCGA) for use in prospective integral biomarker-driven trials in prostate cancer.
Role:	Co-Investigator

U01 CA183027	**(Chinnaiyan, Linehan)**
Title:	**Integrative Molecular Imaging and Sequencing of Prostate Cancer**
Time Commitment:	10% effort, 1.20 calendar
Supporting Agency:	NIH
Grants Officer:	Lori A. Henderson Phone: 240-276-5930 hendersonlori@mail.nih.gov
Performance Period:	02/11/2014-01/31/2017
Level of Funding:	$268,090 annual direct
Project Goals:	1) Enroll patients with known or suspicious for prostate cancer in the NIH MRI/metabolic imaging program, 2) Whole exome and transcriptome sequencing analysis of 60 patients identified with clinically localized prostate cancer from frozen biopsy material obtained in Aim 1. 3) Integrative analysis of histopathology, molecular imaging, metabolism, mutational landscape and gene expression alterations of biopsy material from this clinical trial.
Specific Aims:	Same as above.

UM1 HG006508	**(Chinnaiyan, Pienta, and Robert)**
Title:	**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:	07/19/2013-05/31/2017
Level of Funding:	$813,023 annual direct
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:	*Project 1:* Clinical Genomic Study, 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. *Project 2:* Sequencing, Analysis, and Interpretation of Sequencing Data; 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	**(Chinnaiyan)**
Title:	**Advancing Our Understanding of the Etiologies and Mutational Landscapes of Basal-Like, Luminal A, and Luminal B Breast Cancers**
Time Commitment:	7.58% effort, 0.91 calendar
Supporting Agency:	DOD – Collaborative Innovators Award
Grants Officer:	Cheryl A. Lowery Phone: 301-619-7150 Cheryl.Lowery@us.army.mil
Performance Period:	09/15/2012-09/14/2017
Level of Funding:	$479,470 annual direct
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.

W81XWH-14-1-0555	**(Chinnaiyan, Navone)**
Title:	**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:	09/22/2014-09/21/2017
Level of Funding:	$125,978 annual direct
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.

R01 CA125612	**(Rubin)**
Title:	**Towards Understanding Prostate Cancer Heterogeneity**
Time Commitment:	2% effort, 0.24 calendar
Supporting Agency:	NIH
Grants Officer:	Michelle Lewis, Joan & Sanford I Weill Medical College of Cornell University 1300 York Avenue, New York, NY 10085
Performance Period:	04/01/2013-03/31/2018
Level of Funding:	$27,400 annual direct
Project Goals:	Determine protein-protein interactions and subsequent signaling cascades with mass spectrometry.
Specific Aims:	1) To determine the substrate specificity of prostate cancer-derived SPOP mutants; 2) To determine the downstream pathways deregulated by SPOP mutations; 3) To establish the prevalence of SPOP mutation, its relation to other molecular changes, and its significance to patient outcomes in multiple populations of prostate cancer.
Role:	Co-Investigator

U01 HL126499	**(Tewari)**
Title:	**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:	$101,781 annual direct
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) To sequence exRNAs present in biofluids of healthy individuals. 2) To identify and annotate both endogenously and exogenously-derived exRNA sequences. 3) To perform validation and absolute quantification of exRNAs using droplet digital PCR (ddPCR). 4) To perform cross-validation service and integrate scientifically with other Consortium teams.
Role:	Co-Investigator
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. Project 4: Development of IncRnas 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:	$1,610,903 annual direct
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 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. *Project 4 Aims:* 1) Employ a compendium of prostate cancer RNA-Seq data to nominate IncRNAs for assessment in urine. 2) Develop a urine multiplex panel of IncRNAs (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 IncRNAs in urine for the detection of high grade prostate cancer. In this Aim, we will identify individual IncRNAs or combinations with PGAS+TMPRSS2-ERG that assist in non-invasively detecting high grade prostate cancer in urine. *Core 3 aims:* 1) To protect patient welfare; 2) The acquisition and processing of prostate tissues for research; 3) The maintenance of clinical and pathology data with links to molecular studies; To provide high quality pathologic review of prostate tissues; 5) To provide expert pathology consultation; 6) To perform quality assessment of prostate tissues and clinical data; 7) To 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)

ROBINSON, Dan
ACTIVE

SU2C **(Chinnaiyan)**
Title: **Precision Therapy of Advanced Prostate Cancer**
Time Commitments: 5% effort, 0.60 calendar
Supporting Agency: AACR-PCF-SU2C
Grants Officer: Frederic Biemar
Phone: 215-446-7261
frederic.biemar@aacr.org
Performance Period: 08/01/2012-07/31/2016 (NCTX)
Level of Funding: $538,355 annual direct
Project Goals: The overall goal of this proposal is to catalyze the interaction of a multi-disciplinary team of investigators, with a track record of accomplishments in prostate cancer research, to work together on the challenging problem of metastatic castration resistant prostate cancer (CRPC).
Specific Aims: 1) Establish a multi-institutional infrastructure incorporating 5 leading prostate cancer clinical sites, 2 sequencing and computational analysis sites, linked with appropriate sample and data coordination; 2) Establish a prospective cohort of 500 patients (the "CRPC 500") utilizing the multi-institutional infrastructure to support the clinical use of integrative prostate cancer sequencing, analysis, and clinical trial decision making; 3) Conduct parallel, preclinical in vivo functional studies of resistance biomarkers and of SU2C-PCF sponsored combination therapies; 4) Identify molecular determinants of abiraterone sensitivity and acquired resistance in patients; 5) Conduct clinical trials of novel combinations targeting AR and/or the PTEN pathway, based on existing preclinical data and an understanding of resistance mechanisms; 6) Identify molecular determinants of sensitivity and acquired resistance to PARP inhibitors in patients.
Role: Co-Investigator

PC121111 **(Scher)**
Title: **Toward the Practice of Precision Medicine: Multicenter Validation of Biomarker Assays for Clinical Management of Prostate Cancer**
Time Commitment: 16% effort, 1.92 calendar
Supporting Agency: DOD
Grants Officer: Kathy E. Robinson
820 Chandler Street
Fort Detrick MD 21702-5014
Performance Period: 09/30/2013-09/29/2016
Level of Funding: $300,000 annual direct
Project Goals: Establish and validate TMPRSS2:ERG assays; Validate the utility of the TMPRSS2:ERG TMA assay for the non-invasive detection of

	clinically significant prostate cancer in urine; Validate the ERG rearrangement FISH assay on tissues and determine the prevalence of ERG rearrangements in isolated precursor and diagnostically challenging lesions.
Specific Aims:	1) To cross-validate an initial set of assays for biomarkers corresponding to the AR and PI3K/PTEN axes ready for near-term filing with the FDA for use in prospective integral biomarker-driven trials in prostate cancer; 2) To use the centralized infrastructure of the Assay Validation Coordinating Center to cross-validate additional assays for biomarkers identified via established and emerging discovery platforms (i.e., NCI Prostate Cancer SPOREs, PCF, SU2C, and TCGA) for use in prospective integral biomarker-driven trials in prostate cancer.
Role:	Co-Investigator

U01 CA183027	**(Chinnaiyan and Linehan)**
Title:	**Integrative Molecular Imaging and Sequencing of Prostate Cancer**
Time Commitment:	16% effort, 1.92 calendar
Supporting Agency:	NIH
Grants Officer:	Lori A. Henderson Phone: 240-276-5930 hendersonlori@mail.nih.gov
Performance Period:	02/11/2014-01/31/2017
Level of Funding:	$268,090 annual direct
Project Goals:	1) Enroll patients with known or suspicious for prostate cancer in the NIH MRI/metabolic imaging program, 2) Whole exome and transcriptome sequencing analysis of 60 patients identified with clinically localized prostate cancer from frozen biopsy material obtained in Aim 1. 3) Integrative analysis of histopathology, molecular imaging, metabolism, mutational landscape and gene expression alterations of biopsy material from this clinical trial.
Specific Aims:	Same as above.
Role:	Co-Investigator

UM1 HG006508	**(Chinnaiyan, Pienta, and Robert)**
Title:	**Exploring Precision Cancer Medicine for Sarcoma and Rare Cancers**
Time Commitment:	16% effort, 1.92 calendar
Supporting Agency:	NIH
Grants Officer:	Zephaun Harvey Phone: 301-435-7859 harveyz@mail.nih.gov
Performance Period:	07/19/2013-05/31/2017
Level of Funding:	$813,023 annual direct
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.
Specific Aims:	*Project 1:* Clinical Genomic Study, 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. *Project 2:* Sequencing, Analysis, and Interpretation of Sequencing Data; 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.
Role:	Co-Investigator

W81XWH-14-1-0555	**(Chinnaiyan, Navone)**
Title:	**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:	09/22/2014-09/21/2017
Level of Funding:	$125,978 annual direct
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

W81XWH-12-1-0080	**(Chinnaiyan)**
Title:	**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: 09/15/2012-09/14/2017
Level of Funding: $479,470 annual direct
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

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 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: $186,410 annual direct
Project 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: Co-Investigator

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U01 CA183027 **(Chinnaiyan, Linehan)**
Title: **Integrative Molecular Imaging and Sequencing of Prostate Cancer**
Time Commitments: 35% effort, 4.20 calendar
Supporting Agency: NIH/NCI
Grants Officer: Lori A. Henderson
Phone: 240-276-5930
hendersonlori@mail.nih.gov
Performance Period: 02/11/2014-01/31/2017
Level of Funding: $268,090 annual direct

Goals:	1) Enroll patients with known or suspicious for prostate cancer in the NIH MRI/metabolic imaging program, 2) Whole exome and transcriptome sequencing analysis of 60 patients identified with clinically localized prostate cancer from frozen biopsy material obtained in Aim 1. 3) Integrative analysis of histopathology, molecular imaging, metabolism, mutational landscape and gene expression alterations of biopsy material from this clinical trial.
Specific Aims:	Same as above
Role:	Co-Investigator

W81XWH-14-1-0555	**(Chinnaiyan)**
Title:	**Development of Personalized Cancer Therapy for Men with Advanced Prostate Cancer**
Time Commitments:	20.08% effort, 2.41 calendar
Supporting Agency:	DOD
Grants Officer:	Peggie Lesnow Phone: 301-619-2367 margaret.a.lesnow.civ@mail.mil
Performance Period:	09/22/2014-09/21/2017
Level of Funding:	$125,978 annual direct
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

W81XWH-12-1-0080	**(Chinnaiyan)**
Title:	**Advancing our Understanding of The Etiologies and Mutational Landscapes of Basal-Like, Luminal A, and Luminal B Breast Cancers**
Time Commitments:	10% effort, 1.20 calendar
Supporting Agency:	DOD
Grants Officer:	Cheryl A. Lowery Phone: 301-619-7150 Cheryl.Lowery@us.army.mil
Performance Period:	09/15/2012-09/14/2017
Level of Funding:	$479,470 annual direct
Goals:	Define the Mutational Landscapes of Breast Cancer
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:	Research Specialist
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:	$1,610,903 annual direct
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

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. Partner 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.