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

PRINCIPAL INVESTIGATOR: Dr. Arul M. Chinnaiyan (Partnering PI)

CONTRACTING ORGANIZATION: University of Michigan
Ann Arbor, MI 48109-5940

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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) that are responders and nonresponders to these therapies. We will identify genomic alterations via integrative genomic analysis of these 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.
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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) 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. 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, 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.** 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. Many of these are listed in Passage 0 because they did not produce a tumor large enough to be passaged to a second mouse (Passage 1) (MD Anderson site, Dr. Navone’s Laboratory).

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.
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<th>Clinical Stage</th>
<th>Procedure Type</th>
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**Table 1. Prostate cancer tissue specimen implanted into mice for PDX developed since May 2016**

**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 MET protein level in various prostate cancer cell lines and found MET levels to be higher in AR negative versus AR positive lines. In particular, we noted a higher MET protein level in AR negative 146-10 PDX than in AR positive 146-12 PDX model (Fig. 1).
Fig. 1. MET is highly expressed in AR negative prostate cancer cell lines and PDX models. Western blot analysis of MET protein expression in various prostate cell lines with different AR status and two PDX models.

Fig. 2. MET expression predicts sensitivity to MET inhibitor Cabozantinib (Cabo). Invasion assay was performed in the presence of HGF and/or various treatment doses of Cabo in MET high/low and AR-negative/positive prostate cancer cells for 24 hours.

Based on our cell line data and matching MET/AR status, we can postulate that AR-negative/MET high PDXs (i.e. PDX 146-10), like DU145 and PC3 (Fig. 2), should respond to Cabo, while AR-positive/MET low PDXs (i.e PDX146-12), like VCaP and LNCaP (Fig. 2), should be non-responders. In the future, we will test PDX146-10 and PDX 146-12 Cabo responsiveness in vivo. (University of Michigan, Dr. Chinnaiyan Lab).

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.

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, 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.
Prior to May 2016 (before the ACURO review as 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. Briefly, a preclinical study using cells derived 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. 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 have resumed these studies in May 2016 and the experiments are ongoing.

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: 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, namely ENST00000326324; ENST00000397091; ENST00000397098; ENST00000397113; ENST00000429567 and ENST00000532791 (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.

Since these isoforms are predicted from RNA sequencing, we at the MD Anderson site have first validated these findings by RT-PCR with specific primers using PDXs and prostate cancer cell lines. We subsequently assessed the expression of FGFR1alpha and beta in three prostate cancer cell lines (PC3, DU145 and C4-2B) and seven prostate cancer PDXs (MDA PCa 2b, MDA PCa 118b, MDA PCa 155-12; MDA PCa 146-10; MDA PCa 146-12; MDA PCa 150-3 and MDA PCa 183) derived from primary prostate cancer, bone metastases and brain metastases and reflecting the typical adenocarcinoma as well as, adenocarcinomas with neuroendocrine differentiation and small cell carcinomas of prostate cancer. We found that all PDXs express primarily FGFR1alpha isoform while prostate cancer cell lines express FGFR1beta (Fig. 3).

![Table 2](https://example.com/Table2.png)

**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).

![Fig. 3](https://example.com/Fig3.png)

**Fig. 3.** Levels of FGFR1 alpha and beta mRNA expression in prostate cancer cell lines and prostate cancer PDXs were assayed by RT-PCR.
In transient transfections we studied differences in the signaling pathways activated by the two isoforms. For that we transiently transfected two prostate cancer cell lines, PC3 and C4-2B, with empty vector (EV), FGFR1alpha (NM_023110.2) or FGFR1beta (NM_023105.2). We subsequently treated the cells with vehicle, FGF2 or FGF9 to induce the pathway and analyzed the results by Western blot. We observed that only FGFR1 alpha expression (not FGFR1 beta) results in its phosphorylation and induces PLCγ phosphorylation in both cell lines (Fig. 4). In PC3 cells, we found that total FGFR1 expression (relative to a loading control) was similar in cells transfected with FGFR1beta or FGFR1alpha. Levels of p-FGFR1 were high in untreated cells transfected with FGFR1alpha, but no further induction was observed after treatment with FGF2 or FGF9. However, p-FGFR1 expression was almost undetectable in untreated cells expressing FGFR1beta and was slightly induced by FGF2 but not by FGF9. p-PLCγ expression was found only in cells expressing FGFR1alpha. Similar results were found in C4-2B (Fig. 4).

Further in vitro studies show higher proliferation rates for PC3 cells expressing isoform alpha when evaluated by direct cell counting with Trypan blue exclusion method compared to cells expressing beta and control cells (Fig. 5). Also, invasion assays using Matrigel invasion chambers show that both PC3 cells with alpha and beta isoform invade more than empty vector control cells (data not shown).

*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.*

**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

No changes

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 will compensate this delay in the coming year.
### Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

No changes

### 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

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### 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.
### Participants & Other Collaborating Organizations

**What individuals have worked on the project?**

*The University of Texas MD Anderson Cancer Center*

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<tr>
<th>Name</th>
<th>Project Role</th>
<th>Nearest person month worked</th>
<th>Contribution to Project</th>
<th>Funding Support</th>
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<td>Nora M. Navone</td>
<td>Principal Investigator</td>
<td>1.80 calendar months</td>
<td>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.</td>
<td>Funding support is provided from this award.</td>
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<td>John Araujo</td>
<td>Co-Principal Investigator</td>
<td>0.12 calendar months</td>
<td>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.</td>
<td>Funding support is provided from this award.</td>
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<td>Bradley Broom</td>
<td>Collaborator</td>
<td>0.24 calendar months</td>
<td>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.</td>
<td>Funding support is provided from this award.</td>
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<td>Estefania Labanca</td>
<td>Graduate Research Assistant-GSBS</td>
<td>3.60 calendar months</td>
<td>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.</td>
<td>Salary support will be provided from this grant upon DOD approval.</td>
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<td>Xinhai Wan</td>
<td>Collaborator</td>
<td>4.80 calendar months</td>
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*Funding Support:*

Salary support will be provided from this grant upon DOD approval.
**Contribution to Project:**

Dr. Wan was responsible for intrabone injection of prostate cancer cells in mice and the in vivo experiments involving laboratory animals. He performed the immunohistochemical studies of tissue samples and the molecular and cell biology studies related to the in vivo studies. Dr. Wan trained Estefania Labanca, Graduate Research Assistant, in these techniques before he left and she will be responsible for these studies now.

**Funding Support:**

Funding support was provided from this award up to 7/31/2016 when Dr. Wan left the department to serve as a Sr. Research Scientist. Since he is no longer working with Dr. Navone his effort was removed effective 8/1/2016.

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**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.

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**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.

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**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.

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**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: 2.40 calendar months
Contribution to Project: Provides bioinformatic analysis in the context of candidate gene nominations.
Funding Support: Funding support is provided from this award.

Name: Jean Tien
Project Role: Research Investigator
Nearest person month worked: 2.40 calendar months
Contribution to Project: PDX models
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**

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

Supporting Agency: PCF/Movember
Grants Officer: Dr. Mark Buzza, Movember Foundation-1250 Fourth Street, Santa Monica CA 90401
Time Commitment: 1% effort, 0.12 calendar
Performance Period: 01/01/2014-12/30/2016 NCE
Level of Funding: Not applicable

Goals: The ultimate goal is 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
Role: Principal Investigator
<table>
<thead>
<tr>
<th>Supporting Agency</th>
<th>Performance Period</th>
<th>Level of Funding</th>
<th>Goals</th>
<th>Specific Aims</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>SINF</td>
<td>11/01/2013-11/30/2016</td>
<td>10% effort, 1.20 calendar (unsalaried)</td>
<td>The ultimate goal is not only to obtain a more in-depth understanding of the signaling circuitry that drives osteoblastic bone metastasis in castration-resistant prostate cancer patients, but also to provide a rational basis for the use of FGFR-targeted agents and a model system of anticipated resistance mechanisms.</td>
<td>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.</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>Janssen</td>
<td>08/14/2014-07/31/2017</td>
<td>15% effort, 1.80 calendar</td>
<td>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.</td>
<td>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.</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PCa Moon Shot</td>
<td>05/30/2015-05/29/2017</td>
<td>5% effort, 0.60 calendar</td>
<td>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.</td>
<td>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.</td>
<td>Principal Investigator</td>
</tr>
</tbody>
</table>
Performance Period: 09/01/2016-08/31/2017
Level of Funding:
Goals:

1) To determine the two year cancer free survival of men treated with AA, and androgen ablation + androgen biosynthesis inhibition. 2) To link the outcomes in subproject 1 to the biologic characterization of the primary, blood, of the study patients in goal 1 and pretreated cancers to outcome(s). 3) Initiate two clinical trials in priority targets identified in “curative intent trials“ and apply the findings to develop marker driven combinations or sequences of therapy in select patients.

Specific Aims: Same as above
Role: Co-Investigator

**PCa Moon Shot**
(Logothetis/Thompson)

**Title:** Flagship 2: Targeting the Immune and Non-Immune Tumor-Associated Microenvironments in Prostate Cancer

Time Commitment: 5% effort, 0.60 calendar
Supporting Agency: MD Anderson Moon Shot Program
Grants Officer: Govind Narasimhan, Director, Res. Finance

Performance Period: 09/01/2016-08/31/2017
Level of Funding: The ultimate goal is to rationally integrate bone-targeting agents with immune checkpoint therapies to cure metastatic prostate cancer by continuing to implement our co-clinical approach with novel preclinical models and patient samples acquired from our biomarker-driven clinical trials.

Goals:

Specific Aims: 1) To identify biomarkers within the secretome predictive of responsiveness to cabozantinib. 2) To identify biomarkers within the bone secretome predictive for earlier clinical intervention with radium-223 in patients with metastatic prostate cancer to the bone and in combination with other targeted therapies. 3) To rationally integrate immune checkpoint strategies with cabozantinib and radium-223.

Role: Co-Investigator

**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-PCRP Synergistic Idea Development Award
Grants Officer: Janet P. Kuhns
Performance Period: 09/22/2014-09/21/2017
Level of Funding: 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.

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: Principal Investigator

R01 CA193362-01A1 (Yang)
Title: Role of Integrin VLA-6 in Suppression of Bone Formation in Myeloma
Time Commitment: 5% effort, 0.60 calendar
Supporting Agency: NIH/NCI
Grants Officer: LeSchell D. Browne, Grants Management Specialist
Performance Period: 02/01/2016-01/31/2021
Level of Funding:
Goals: 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 α6 integrin in myeloma cells enhances adipogenesis and suppresses osteoblastogenesis and bone formation. 2) Determine whether α6 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 CA140388-06A1 (Logothetis/Thompson)
Title: MD Anderson Cancer Center Prostate Cancer SPORE – Core 2: Biospecimen and Pathology Core
Time Commitment: 5% effort, 0.60 calendar
Supporting Agency: NIH/NCI
Grants Officer: Leslie Hickman
Performance Period: 09/01/2016-08/31/2021
Level of Funding:
Goals: The overall 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 patient-derived xenografts) 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 (Prometheus) that tightly integrates biospecimen acquisition, annotation, and analysis workflows with clinical data in a secure and accessible manner.
Role: Co-Investigator, Core 2

Overlap: None
ARAUJO, John
CURRENT

2 P50 CA140388-06A1 (Logothetis and Thompson)

MD Anderson Cancer Center Prostate Cancer SPORE.

Project 2: Targeting Tumor Microenvironment-induced Therapy Resistance in Prostate Cancer Bone Metastasis

Title: MD Anderson Cancer Center Prostate Cancer SPORE.

Time Commitment: 5%, 0.60 CM
Supporting Agency: NIH/NCI
Grants Officer: Leslie Hickman,
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

PCa Moon Shot Program (Logothetis and Thompson)

MD Anderson Moon Shot Program

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 Cancer Center, Prostate Cancer Moon Shot
Grants Officer: Claudia Delgado, Executive Director, Grants and Contracts

Performance Period: 09/01/2016-08/31/2017
Level of Funding: 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.

Same as above

Specific Aims: Co-Investigator
Role:
Development of Personalized Cancer Therapy for Men with Advanced Prostate Cancer

2% effort, 0.24 calendar

DOD-PCRP Synergistic Idea Development Award

Janet P. Kuhns, Contracting Officer

Performance Period: 09/22/2014-09/21/2017

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

Cancer Center Support Grant

39% effort, 4.68 calendar

NIH/NCI

Hasnaa Shafik, Program Director

Performance Period: 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.

Specific Aims: Same as above.
Role: Co-Investigator

MD Anderson Cancer Center Bioinformatics Gift

15.08% effort, 1.81 calendar

Michael and Susan Dell Foundation
Aliya Hussaini
P.O. Box 163867
Austin, TX 78716

Performance Period: 04/25/2011-10/04/2017

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.
Specific Aims: The projects under way are largely, but not exclusively focused on non-small cell lung cancer.
Role: Investigator

P50 CA140388-06A1 (Logothetis and Thompson)
Title: MD Anderson Cancer Center Prostate Cancer SPORE Core 1: Biostatistics and Bioinformatics

Time Commitment: 13.5% effort, 1.62 calendar
Supporting Agency: NIH/NCI
Grants Officer: Leslie Hickman
Performance Period: 09/01/2016-08/31/2021
Level of Funding:

Project Goals: The Biostatistics and Bioinformatics Core provides comprehensive biostatistic and bioinformatic expertise to ensure statistical integrity and optimize data analysis for the studies in the 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-Investigator

OVERLAP: None

UNIVERSITY OF MICHIGAN KEY PERSONNEL

CHINNAIYAN, Arul M.
CURRENT U01 CA214170 (Chinnaiyan, Tomlins)
Title: 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
Performance Period: 09/01/2016-08/31/2021
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.

R01 CA200660  
(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 |
| Performance Period: | 08/01/2016-07/31/2021 |

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.

U24 CA210967  
(Nesvishkii and Chinnaiyan)  
University of Michigan Proteogenomics Data Analysis Center  

| Time Commitment: | 8% effort, 0.96 calendar |
| Supporting Agency: | NIH |
| Grants Officer: | Rodriguez, Henry |
| Performance Period: | 09/15/2016-08/31/2021 |

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.

U01 CA183027
Title: (Chinnaiyan, Linehan) Integrative Molecular Imaging and Sequencing of Prostate Cancer
Time Commitment: 10% effort, 1.20 calendar
Supporting Agency: NIH
Grants Officer: Lori A. Henderson
Performance Period: 02/11/2014-01/31/2017
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
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
Performance Period: 07/19/2013-05/31/2017
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:
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 multidisciplinary 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.

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**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:** 7.50% effort, 0.90 calendar

**Supporting Agency:** DOD – Collaborative Innovators Award

**Grants Officer:** Cheryl A. Lowery

**Performance Period:** 09/15/2012-09/14/2017

**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.

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**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

**Performance Period:** 09/22/2014-09/21/2017

**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.
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  
**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) 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  
**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 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)

OVERLAP: None

ROBINSON, Dan
CURRENT

U01 CA183027 (Chinnaiyan and Linehan)
Title: Integrative Molecular Imaging and Sequencing of Prostate Cancer
Time Commitment: 7% effort, 0.84 calendar
Supporting Agency: NIH
Grants Officer: Lori A. Henderson
Performance Period: 02/11/2014-01/31/2017
Level of Funding:
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: 15% effort, 1.80 calendar
Supporting Agency: NIH
Grants Officer: Zephau Harvey
Performance Period: 07/19/2013-05/31/2017
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.

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

**Performance Period:** 09/22/2014-09/21/2017

**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.

**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

**Performance Period:** 09/15/2012-09/14/2017

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

**Project Goals:**

**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
Performance Period: 09/11/2014-08/31/2019
Level of Funding:

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

OVERLAP: None

WU, Yi-Mi
CURRENT
U01 CA183027 (Chinnaiyan, Linehan)
Title: Integrative Molecular Imaging and Sequencing of Prostate Cancer

Time Commitments: 20% effort, 2.40 calendar
Supporting Agency: NIH/NCI
Grants Officer: Lori A. Henderson

Performance Period: 02/11/2014-01/31/2017
Level of Funding:
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
W81XWH-12-1-0080
(Chinnaiyan)

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

Performance Period: 09/15/2012-09/14/2017
Level of Funding:
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)

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

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.