

AWARD NUMBER: W81XWH-14-1-0466

TITLE: Clonal Evaluation of Prostate Cancer by ERG/SPINK1 Status to Improve Prognosis Prediction

PRINCIPAL INVESTIGATOR: Scott A. Tomlins, M.D., Ph.D.

CONTRACTING ORGANIZATION: University of Michigan
Ann Arbor, MI 48109

REPORT DATE: October 2015

TYPE OF REPORT: Annual

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

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

1. REPORT DATE October 2015			2. REPORT TYPE Annual		3. DATES COVERED 17 Sept 2014 - 16 Sept 2015	
4. TITLE AND SUBTITLE Clonal Evaluation of Prostate Cancer by ERG/SPINK1 Status to Improve Prognosis Prediction					5a. CONTRACT NUMBER	
					5b. GRANT NUMBER W81XWH-14-1-0466	
					5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Scott A. Tomlins E-Mail: tomlinss@umich.edu					5d. PROJECT NUMBER	
					5e. TASK NUMBER	
					5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Regents of the University of Michigan 3003 S. State Street Ann Arbor, MI 48109					8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012					10. SPONSOR/MONITOR'S ACRONYM(S)	
					11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited						
13. SUPPLEMENTARY NOTES						
14. ABSTRACT Prostate cancer is commonly multiclonal, meaning that most men with prostate cancer have multiple, genetically distinct cancers. Pathologists cannot assess clonality by routine microscopic evaluation, and hence multiclonality is not incorporated into routinely reported pathological parameters, such as the number of cores with cancer. Given the importance of routine pathological parameters in prostate cancer prognosis, the potential to refine these parameters through assessing multiclonality represents a major opportunity. Hence, the objectives of this proposal are to utilize dual ERG/SPINK1 immunohistochemistry (IHC)—which can identify clonal, mutually exclusive molecular subtypes—to assess the frequency of multiclonality in key clinical scenarios at biopsy and resection and its impact on prognostic parameters. Herein we confirm multiclonality in key diagnostic scenarios, such as discontinuous involvement of a single biopsy core. We anticipate that continued investigation will demonstrate the importance of incorporating multifocality in routine pathology practice.						
15. SUBJECT TERMS Multiclonality, ERG, SPINK1, immunohistochemistry, active surveillance, prostate biopsy, prostatectomy						
16. SECURITY CLASSIFICATION OF:				17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT	b. ABSTRACT	c. THIS PAGE	19b. TELEPHONE NUMBER (include area code)			
Unclassified	Unclassified	Unclassified	Unclassified	23		

Table of Contents

	<u>Page</u>
1. Introduction.....	4
2. Keywords.....	4
3. Accomplishments.....	4-8
4. Impact.....	8
5. Changes/Problems.....	8-9
6. Products.....	9
7. Participants & Other Collaborating Organizations.....	9-11
8. Special Reporting Requirements.....	11
9. Appendices.....	12-23

INTRODUCTION:

Prostate cancer is commonly multiclonal (also referred to as multifocal), meaning that more than 80% of men with prostate cancer actually have multiple, genetically distinct cancers in their prostate. Pathologists cannot assess focus clonality by routine microscopic evaluation, and hence multiclonality is not incorporated into routinely reported pathological parameters, such as the number of biopsy cores with cancer. Given the importance of routine pathological parameters in predicting the extent and behavior of prostate cancer, the potential to refine these parameters through assessing multiclonality represents a major opportunity. Hence, the objectives of this proposal are to utilize dual ERG/SPINK1 immunohistochemistry (IHC)—which can identify clonal, mutually exclusive molecular subtypes—to assess the frequency of multiclonality in key clinical scenarios at biopsy and resection. Secondly, we aim to determine the impact of multiclonality on the ability of pathological parameters at biopsy to predict pathology at resection or outcome after resection. We hypothesized that incorporating multiclonality by IHC evaluation will improve the predictive ability of pathological parameters, and in doing so, will increase the number of men eligible for active surveillance, enhancing the well-being of men with prostate cancer through minimizing over-treatment and treatment-related side effects.

KEYWORDS:

Multiclonality, ERG, SPINK1, immunohistochemistry, active surveillance, prostate biopsy, prostatectomy

ACCOMPLISHMENTS:

What were the major goals of the project?:

SPECIFIC AIMS

- 1) Assess the frequency of multiclonality in clinically important scenarios using dual ERG/SPINK1 IHC.
- 2) Determine whether multiclonality assessment at biopsy improves prediction of pathology at prostatectomy.
- 3) Assess whether multiclonality assessment of index foci at prostatectomy improves outcome prediction.

What was accomplished under these goals?

To accomplish these aims, we developed a tri-institutional collaboration between Drs. Tomlins (PI; University of Michigan [UM]), Larry True (University of Washington [UW]) and Juan Miguel Mosquera (Weill Cornell Medical College). Our proposed statement of work was essentially the same for each site, with the exception of 100 cases to be scanned at the University of Michigan and reviewed by Drs. True and Mosquera (original UM, UW and WCMC statements of work Specific Aim 1.4.c). Likewise, data will be transferred from UW and MCMC to UM for analysis in the third year of the award (UM, UW and WCMC statements of work, Specific Aim 2.3 and 3.3). Hence, progress at each site is reported using the UM statement of work. Progress is described in italics.

Specific Aim 1: Assess the frequency of multiclonality in clinically important scenarios using dual ERG/SPINK1 IHC.

- 1) Obtain study IRB and DoD HRPO approval (months 1-2).

UM has received local IRB and DoD HRPO approval. Although both UW and WCMC had previous local IRB approval for the type of study described herein, local IRB review took much longer than anticipated, significantly delaying additional progress in areas specifically related to this project. Dr. Larry True received local IRB approval after multiple rounds of revision to his application on 09/09/2015. This application has been submitted for HRPO approval, which is pending. Dr. Mosquera received local IRB approval on 3/28/15 and the application was submitted for HRPO submission, however HRPO determined that separate local IRB approval specifically for this project was required prior to HRPO approval. Hence, Dr. Mosquera has resubmitted a separate application to his local IRB, which was granted expedited status on 10/12/15 and is now pending approval. Upon approval, this application will be resubmitted to the HRPO.

Overall, this task is approximately 80% completed.

- 2) Retrospectively identify and review eligible cases (months 3-18)
 - a. Retrospectively identify and review biopsy cases (n=100) from pathology database with discontinuous involvement (months 3-18).
 - b. Retrospectively identify and review biopsy cases (n=100) from pathology database with Gleason score 6 or 3+4=7 and 2-5 positive cores (months 3-18).
 - c. Retrospectively identify and review cases (n=134) from pathology database with Gleason score 3+4=7 at prostatectomy (months 3-18).

After local IRB and HRPO approval, Dr. Tomlins has performed a retrospective search through the UM institutional prostate cancer tissue bank, identifying and reviewing 32 discontinuously involved prostate biopsy cores. An additional 103 cases were identified to evaluate for potential discontinuous involvement that fulfilled the following clinical criteria: 1) Gleason score 6 or 3+4=7 on biopsy; 2) 1-5 cores involved on biopsy; and 3) at least one core >50% involvement. Importantly, this is the group of patients where potential discontinuous involvement would drive clinical management. Review of these cases is ongoing and approximately 30% complete.

Likewise, we have identified a total of 277 cases to evaluate for multiclonality in multiple positive cores that fulfilled the following clinical criteria: 1) Gleason score 6 or Gleason 3+4=7 on biopsy; 2) 1-5 cores involved on biopsy and the patient underwent prostatectomy at UM. Review of these cases is ongoing and approximately 20% complete. Lastly, we have identified 738 cases to evaluate for multiclonality at prostatectomy that fill the following clinical criteria: 1) Gleason score 3+4=7 or 4+3=7 with at least 3 yrs PSA follow-up. Review of these cases is ongoing and approximately 20% complete.

Given that HRPO approval has not been granted for Drs. True and Mosquera, they have not been able to perform these retrospective searches or review in the context of this

project. Both have been provided with the same criteria used by Dr. Tomlins and will complete these searches and review cases upon HRPO approval.

Overall, these tasks are approximately 20% completed.

- 3) Prospectively identify and review eligible biopsy cases
 - a. Prospectively identify and review biopsy cases (n=34) with discontinuous involvement (months 3-32).
 - b. Prospectively identify and review biopsy cases (n=34) from pathology database with Gleason score 6 or 3+4=7 and 2-5 positive cores (months 3-32).

All three sites have been identifying and reviewing biopsy cases as part of their routine clinical practice. At the University of Michigan, we have been logging these cases and entering clinical information into our common database structure. We have identified a total of 13 discontinuously involved biopsies and 22 cases meeting criteria 3.b. Formal review of cases and data input has not been performed at UW and WCMC but will be completed upon HRPO approval of their protocols.

These tasks are approximately 25% completed.

- 4) Perform ERG/SPINK1 dual IHC
 - a. Perform dual ERG/SPINK1 IHC on retrospectively and prospectively identified cases (n=402) identified and reviewed above (months 6-32).
 - b. Evaluate dual ERG/SPINK1 IHC (months 7-32).
 - c. Scan 100 cases for evaluation by Drs. True and Mosquera (months 12-14).

*As only UM has HRPO approval, we have performed and evaluated dual ERG/SPINK1 IHC on a total of 45 UM cases of discontinuously involved prostate cancer biopsy cores, identifying discordant ERG/SPINK1 status by IHC in 3 cases (6%), consistent with multiclonality and supportive of the findings in our preliminary results. This approach, which can refine tumor volume estimation through the identification of discordant ERG/SPINK1 status indicative of involvement by two small tumor foci, is shown in **Figure 1A&B**. Examples of cases with concordant ERG/SPINK1 status in both tumor foci are shown in **Figure 1C &D**.*

*Of note, one of the discordant cases (shown in **Figure 2**), was from a man with 6 cores of high grade cancer on the right side, and one 95% discontinuously involved core with Gleason score 3+3=6 cancer on the left. Although the discontinuous core did not drive the decision to undergo prostatectomy, nerve sparing was not performed on the left side given the concern for high volume disease. As shown in **Figure 2**, ERG/SPINK1 IHC demonstrated that one focus was ERG+/SPINK1-, while the other was ERG-/SPINK1-, consistent with multiclonal disease and two very small foci of individual foci of cancer. Had this information been known prior to prostatectomy, the patient would have been able to undergo nerve sparing on the left side, potentially dramatically improving the patient's quality of life. Lastly, we have performed dual ERG/SPINK1 IHC on 11 cases with 2 involved cores, due to our desire to batch staining of these cases and including more than one core on a section to be stained to save on reagent costs. In this*

preliminary cohort, no cases showed discordant ERG/SPINK1 status, but all cases were evaluable. Cases are being archived for scanning for review by Drs. True and Mosquera after HRPO approval.

Dual ERG/SPINK1 IHC on additional reviewed UM discontinuously involved cores, multiply involved cores, and reviewed prostatectomy cases is ongoing. IHC of UW and WCMC cases will proceed after HRPO approval and review.

Overall, these tasks are approximately 8% completed.

Specific Aim 2: Determine whether multiclonality assessment at biopsy improves prediction of pathology at prostatectomy.

- 1) Input clinicopathological data into common database for cases stained and evaluated above (months 4-32).
- 2) Input ERG/SPINK1 dual IHC data into common database for cases stained and evaluated above (months 4-32).
- 3) Assess associations between extent tumor involvement and number of positive cores with and without multiclonality incorporation and parameters associated with significant pathology at prostatectomy (months 32-34)
- 4) Prepare manuscript on study (months 34-36)

We have modified data fields from pre-existing databases at each institution to enable recording of common data elements and dual ERG/SPINK1 staining results. Information for all stained UM cases has been entered into the local modified database. Information from additional UM cases and UW and WCMC cases (after HRPO approval) will be entered upon staining as described in Aim 1.

These tasks are approximately 10% completed.

Specific Aim 3: Assess whether multiclonality assessment of index foci at prostatectomy improves outcome prediction.

- 1) Input clinicopathological data into common database for cases stained and evaluated above (months 4-32).
- 2) Input ERG/SPINK1 dual IHC data into common database for cases stained and evaluated above (months 4-32).
- 3) Assess associations between Gleason score and tumor volume with and without multiclonality incorporation and PSA recurrence (months 32-34)
- 4) Prepare manuscript on study (months 34-36)

We have modified data fields from pre-existing databases at each institution to enable recording of common data elements and dual ERG/SPINK1 staining results. Information for all stained UM cases has been entered into the local modified database. Information from additional UM cases and UW and WCMC cases (after HRPO approval) will be entered upon staining as described in Aim 1.

These tasks are approximately 10% completed.

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?

The major barrier to achieving our goals has been obtaining local IRB and HRPO approval from all three participating sites. UM has full approval on progress is proceeding as expected. Dr. True has recently submitted his IRB approval for HRPO approval (latest correspondence 10/13/15 when human subjects research training was confirmed). Likewise Dr. Mosquera has received notification of expedited review from his local IRB. Upon HRPO approval, we expect to rapidly identify cases and expect to complete the remaining tasks as stated in the original statement of work. Importantly, dual ERG/SPINK1 staining has been performed at UM and we are batching staining when large numbers of samples are ready to save on reagent costs.

IMPACT:

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

Nothing to Report

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

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

As described above, we have had significant delays obtaining local IRB and HRPO for all three participating sites. However, as described above, we anticipate HRPO approval shortly for UW

and local IRB/HRPO approval for WCMC. We do not anticipate any additional problems beyond these approval issues.

Changes that had a significant impact on expenditures

Distribution of funds from UM to WCMC and UW was delayed while waiting for HRPO approval. Likewise, given the delay in accumulating cases and the somewhat short stability of some IHC components, we have delayed some antibody/staining components while waiting for case numbers to increase.

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

Nothing to Report

PRODUCTS:

Publications, conference papers, and presentations

Nothing to Report

Website(s) or other Internet site(s)

Nothing to Report

Technologies or techniques

Nothing to Report

Inventions, patent applications, and/or licenses

Nothing to Report

Other Products

Nothing to Report

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Scott Tomlins
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person	1

month worked:	
Contribution to Project:	Dr. Tomlins has led all aspects of the study as the PI, including directing database queries at UM, reviewing cases and over-seeing dual ERG/SPINK1 immunohistochemistry. Dr. Tomlins has also assisted in the IRB/DOD HRPO submissions for WCMC and UW.
Funding Support:	

Name:	Juan Miguel Mosquera
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1
Contribution to Project:	Dr. Mosquera has pursued local IRB approval and HRPO approval for the WCMC site.
Funding Support:	

Name:	Larry True
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1
Contribution to Project:	Dr. True has pursued local IRB approval and HRPO approval for the WCMC site.
Funding Support:	

Note: although working less than 1 person month, Dr. Nallasivam Palanisamy who was identified in the original submission as the personnel who would be performing IHC at UM is no longer with the University. He has been replaced by Connie Brenke, who is now performing the staining which is ongoing (as shown in **Figures 1&2**).

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

Please see the Appendix for updated Other Support documents for Drs. Tomlins, Mosquera and True. New and Ended support is indicated for each investigator.

▪ **What other organizations were involved as partners?**

As in original submission

University of Washington
1959 NE Pacific St
Seattle, Washington 98036
Collaborator (Dr. Larry True, Co-I)

Joan & Sanford Weill Cornell Medical College
1300 York Ave
New York, New York 10065
Collaborator (Dr. Juan Miguel Mosquera, Co-I)

SPECIAL REPORTING REQUIREMENTS

Collaborative Awards:

N/A

Quad Charts:

N/A

APPENDICES (see next page):

Figures 1 and 2

Updated Other Support for Dr. Tomlins

Updated Other Support for Dr. Mosquera

Updated Other Support for Dr. True

Figure 1

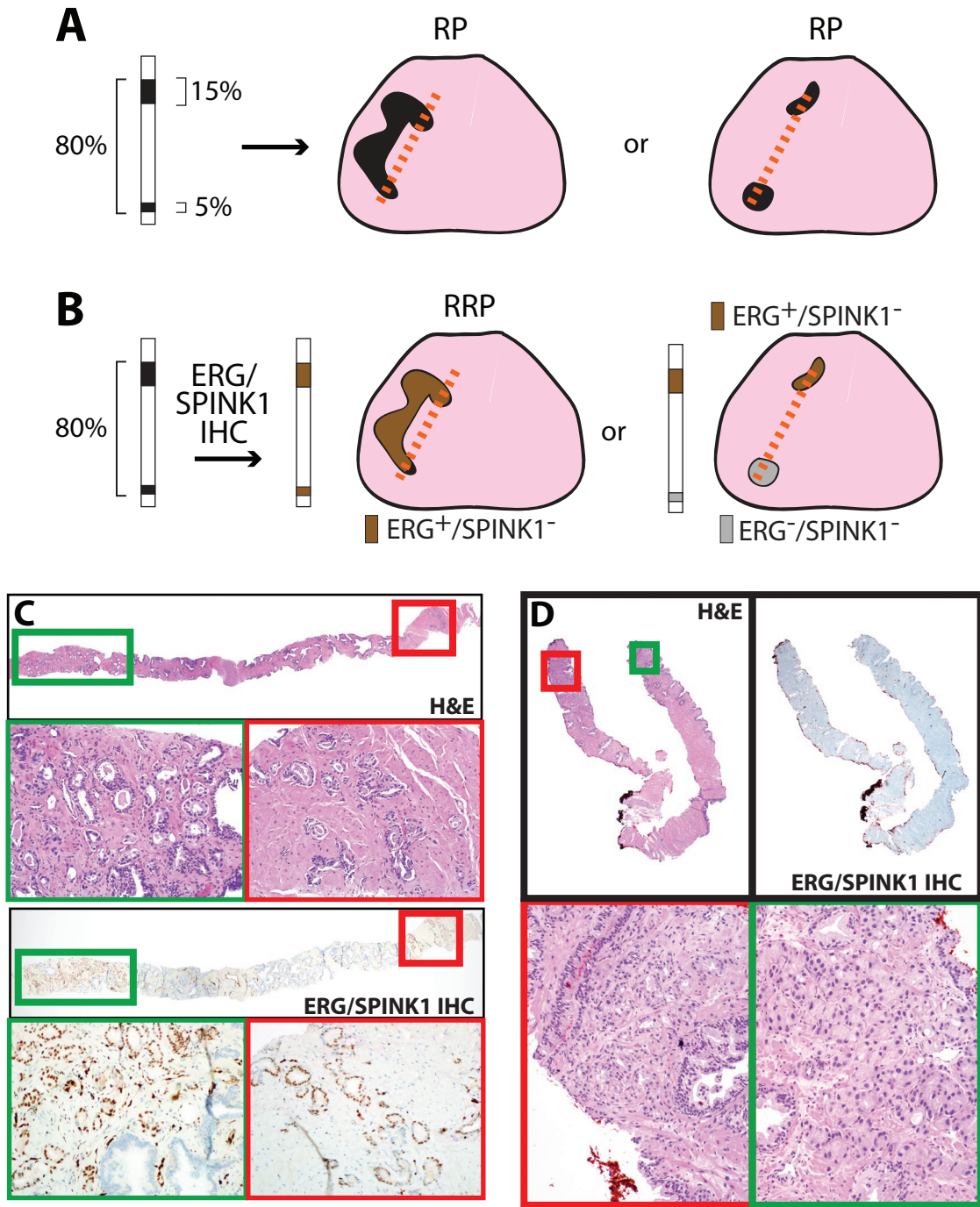


Figure 1. Clonal evaluation of multifocal prostate cancer through ERG/SPINK1 dual immunohistochemistry (IHC). Multifocality due to true multiclonality is common in prostate cancer, but is not assessed in routine pathologic analysis. Our proposal aims to use dual ERG/SPINK1 IHC to determine the impact of multifocality in critical areas where it may impact prognosis, including discontinuously involved biopsy cores (as shown in A). A discontinuously involved cores (black indicates cancer foci) can be assessed by including intervening benign tissue (*i.e.* 80%, left side) or including only cancer (*i.e.* 15%+5%, right side). The former assumes that both foci are from the same tumor clone (biopsy core path schematically represented in orange) as visualized at radical prostatectomy (RP). The latter assumes the foci are from separate clones. **B.** ERG⁺/SPINK1⁻, ERG⁻/SPINK1⁻ and ERG⁻/SPINK1⁺ prostate cancer represent essentially mutually exclusive molecular prostate cancer subtypes. Discordant ERG/SPINK1 status in spatially distinct foci would confirm the presence of smaller, clonally distinct tumors at RP (schematic representation of two molecularly distinct tumors in different colors according to the legend). **C&D.** Examples of Hematoxylin and eosin (H&E) stained and dual ERG/SPINK1 IHC discontinuously involved prostate biopsy cores from two cases are shown. In C, both tumor foci (green and red boxes) were ERG⁺/SPINK1⁻ consistent with concordant involvement and likely clonality. In D, both tumor foci (green and red boxes) were ERG⁻/SPINK1⁻ consistent with concordant involvement and likely clonality.

Figure 2

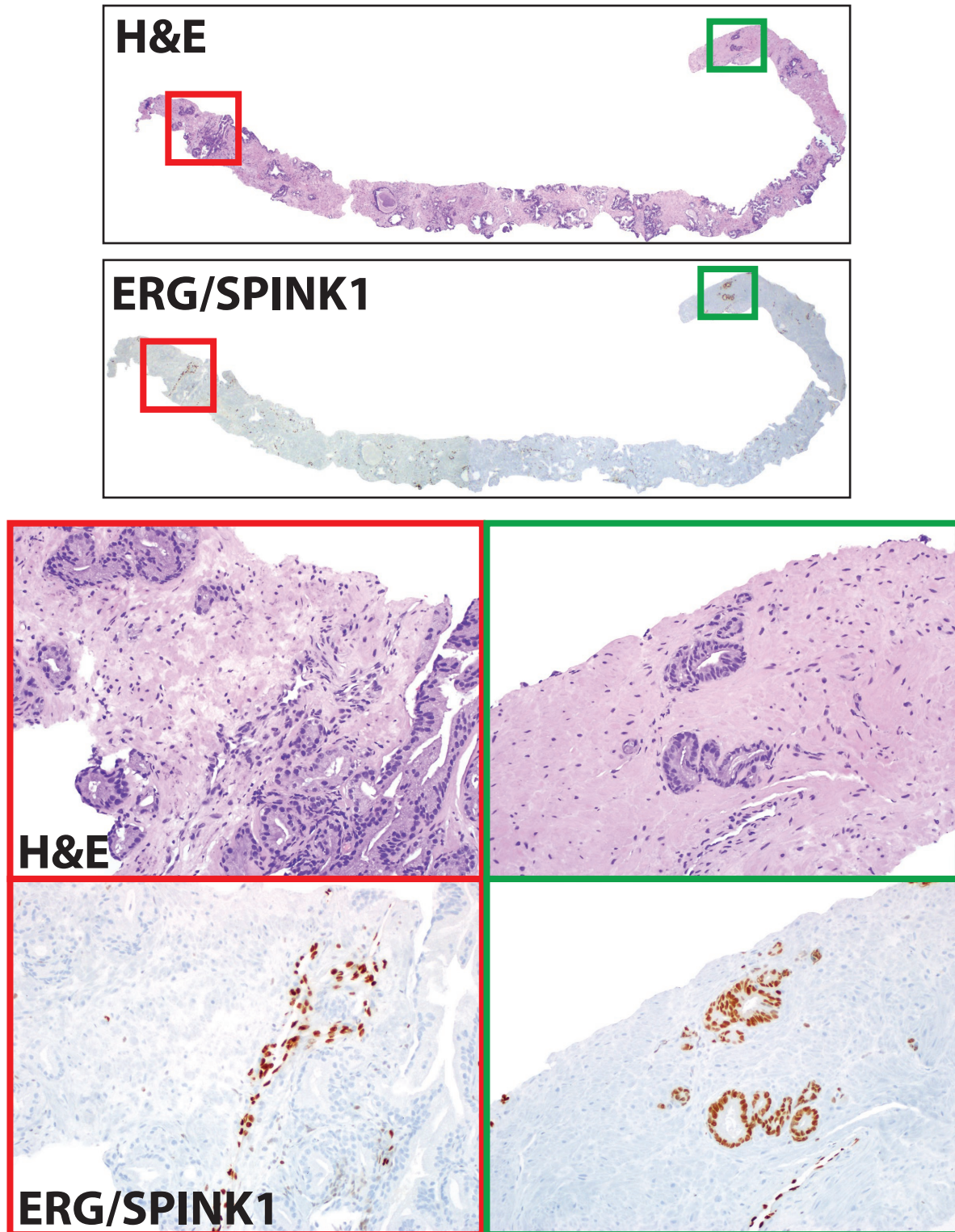


Figure 2. Identification of two clonally distinct tumor foci on a discontinuously involved prostate needle biopsy core by dual ERG/SPINK1 IHC. H&E staining identified two separate tumors that discontinuously involved >90% of one core in this case. IHC staining shows discordant ERG/SPINK1 status between foci (ERG, brown chromogen, nuclear localization; SPINK1, red chromogen, cytoplasmic localization). **A.** One focus is ERG⁺/SPINK⁻ (right) and the other one is ERG⁻/SPINK⁺ (left), consistent with distinct clonal origins and supporting involvement by two small, clinically insignificant tumors rather than a large single tumor.

**UPDATED ACTIVE OTHER SUPPORT:
TOMLINS, SCOTT**

ACTIVE

NEW: PC141474 (PI: Tomlins and Schaeffer) 09/30/15 – 09/29/18 1.2 cal mos

Department of Defense

Comprehensive Molecular Profiling of African-American Prostate Cancer to Inform on Prognosis and Disease Biology

Goal(s): Comprehensively assess molecular alterations in prostate cancer arising in African American men

Specific Aims: 1) Perform comprehensive expression profiling of PCa in AA men to assess the performance of PCa prognostic gene expression signatures; 2) Characterize known and novel PCa gene fusions in AA men; 3) Characterize known and novel PCa mutations and CNAs in AA men to develop an integrated prognostic signature.

Contact Information at funding agency: Tom Winter, Grants Specialist, U.S. Army Medical Research Acquisition Activity, Phone: 240-357-1590 or 301-619-2665, Thomas.s.winter2.civ@mail.mil

NEW: P50CA186786 (PI: Chinnaiyan) 09/11/14 - 08/31/19 1.5 cal mos

NIH

SPORE in Prostate Cancer

Overview: This application consists of four multidisciplinary projects: Project 1: A Precision Medicine Approach to Elucidate Mechanisms of Progression and Resistance to Therapy in Advanced PCa; Project 2: Mechanisms of Sensitivity and Resistance to Cabozantinib in CRPC; Project 3: Development of Novel BET Bromodomain Inhibitors for the Treatment of Advanced PCa; Project 4: Development of IncRNAs as PCa Biomarkers in Urine. These projects are complemented by ongoing, successful Career Development and Developmental Research Programs.

Specific Aims Project 2: 1) Determine if clinical response to CABO in men with CRPC is associated with inhibition of MET/VEGFR/RET signaling. 2) Assess the role of the microenvironment in conferring sensitivity and resistance to CABO; 3) Interrogate the role of tumor genotype and phenotype in conferring sensitivity and resistance to CABO

Specific Aims Project 4: 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 PCA3 and Schlap1) 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.

Contact Information at funding agency: Andrew Hruszkewycz, 301-496-8528, hruszkea@mail.nih.gov

Role: Co-Leader of Project 2; Co-I of Project 4; of Core 3 (Tissue Core)

NEW: R01CA183857 (PI: Tomlins) 04/03/14 - 02/28/19 2.28 cal mos

NIH

Exploiting drivers of androgen receptor signaling negative prostate cancer for precision medicine

Goal(s): Identify novel potential drivers of AR- prostate cancer through sequencing xenografts and tissue samples. Qualify novel drivers of AR- prostate cancer through in vitro models. Develop novel treatment strategies for AR- and AR+ prostate cancer through in vivo models.

Specific Aims: 1) Identify novel potential drivers of AR- prostate cancer. 2) Qualify novel drivers of AR- prostate cancer through in vitro models. 3) Develop novel treatment strategies for AR- and AR+ prostate cancer through in vivo models exploiting AR- drivers.

Contact information at Funding Agency: Morrow, Charles, 301-451-4467 morrowcs@csr.nih.gov

NEW: U01 CA179106 (Hadjiyski)

05/15/14 - 04/30/18

0.6 cal mos

NIH

Biomarkers for Staging and Treatment Response Monitoring of Bladder Cancer

Goal(s): The goal of this project is to develop effective decision support tools that merge image-based and non-image-based biomarkers to assist radiologists and oncologists in assessment of cancer stage and change as a result of treatment.

Specific Aims: To develop QIBC to assist radiologists in evaluation of bladder GTV on multimodality images (MM-bladder tumors); To develop decision support systems to assist clinicians in staging and monitoring of treatment response of bladder cancer by using image biomarkers, pathological information and diagnostic test results, and immunohistochemical biomarkers; To evaluate the effects of QIBC and CDSS-T on clinicians' inter-observer variability, efficiency and accuracy in estimation of bladder GTV and tumor treatment response by observer studies; To evaluate the CDSS-S and CDSS-T as clinical decision support tools for estimation of tumor treatment response in pilot clinical studies.

Contact information at funding agency: Emily Tran, Email: trane@mail.nih.gov Phone: (240) 276-6324 Fax: 301-496-8601

Role: Co-Investigator

NEW: W81XWH-14-1-0466 (PI: Tomlins)

09/17/14 – 09/16/17

0.84 cal mos

Department of Defense

Clonal Evaluation of Prostate Cancer by ERG/SPINK1 Status to Improve Prognosis Prediction

Goal(s): Utilize ERG/SPINK1 status to assess the frequency of multiclonality in clinically relevant scenarios and to determine whether incorporating tumor clonality improves prognostic prediction.

Specific Aims: To develop QIBC to assist radiologists in evaluation of bladder GTV on multimodality images (MM-bladder tumors); To develop decision support systems to assist clinicians in staging and monitoring of treatment response of bladder cancer by using image biomarkers, pathological information and diagnostic test results, and immunohistochemical biomarkers; To evaluate the effects of QIBC and CDSS-T on clinicians' inter-observer variability, efficiency and accuracy in estimation of bladder GTV and tumor treatment response by observer studies; To evaluate the CDSS-S and CDSS-T as clinical decision support tools for estimation of tumor treatment response in pilot clinical studies.

Contact information at funding agency: Emily Tran, Email: trane@mail.nih.gov Phone: (240) 276-6324

UM1HG006508 (PI: Chinnaiyan)

07/19/13 – 05/31/17

0.24 cal mos

National Institutes of Health

Salary support only

Exploring Precision Cancer Medicine for Sarcoma and Rare Cancers

Goal(s): 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.

Role: Co-Investigator

Contact Information at funding agency: Harvey, Zephaun, harveyz@mail.nih.gov, 301 435-7859

Award No. N/A (PI: Knudsen/Feng/Tomlins)

12/01/13 - 11/30/15

0 cal

mos Prostate Cancer Foundation

Targeting DNA Repair Alterations To Improve Treatment for Advanced Prostate Cancer

Goal(s): Comprehensively interrogate DNA repair alterations in both AR-positive and AR-negative CRPC to develop novel biomarkers and therapeutic strategies with the goal of improving outcomes for patients with these aggressive diseases

Specific Aims: 1) Determine the molecular and cellular consequence of tumor-associated DNAPK dysregulation; 2) Assess the impact of targeting DNAPK and the DDR on tumor progression & therapeutic response; 3) Targeting AR-mediated DNA repair through the requisite cofactor USP22; 4) Profiling DNA repair alterations in AR-negative, late stage disease.

Role: Co-PI (Study supervision without funded effort)

Contact Information at funding agency: Audrey Gardner, PCF Applications (applications@pcf.org)

W81XWH-13-1-0371 (PI: Cooney)

09/30/13 - 09/29/16

1.44 cal mos

Department of Defense

High throughput sequencing of germline and tumor from men with early-onset, metastatic prostate cancer

Goal(s): To perform next generation sequencing on germline DNA, prostate cancer, and normal prostate tissue on samples from men with early-onset, clinically significant disease.

Specific Aims: 1. To identify and clinically characterize a set of 20 men who present with Stage 4 (Tx N1 and/or M1) prostate cancer at an early age defined as at or before age 60, and 2. To interrogate the germline exome and tumor exome/transcriptome from 20 men with early-onset Stage 4 prostate cancer to identify novel molecular alterations that may contribute to the early-onset, aggressive prostate cancer.

Role: Co-Investigator

Contact Information at Funding Agency: Kathy E. Robinson, Grants Officer, Us Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick Md 21702-5014

PC121111 (PI: Scher, H.)

09/30/13 – 09/29/16

0.24 cal

mos Department of Defense

Toward the Practice of Precision Medicine: A Biomarker Validation Coordinating Center

Goal(s): Establish Multicenter Validation of Biomarker Assays for Clinical Management of Prostate Cancer and validate TMRSS2:ERG assays; Validate the utility of the TMRSS2: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

Contact Information at Funding Agency: Kathy E. Robinson, Grants Officer, Us Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick Md 21702-5014

R01 CA181605 (PI: Nelson)

01/01/14 - 12/31/15

0.96 cal mos

NIH

Non Invasive Biomarkers for Diagnosing Clinically Significant Prostate Cancer

Goal(s): Test the hypothesis that biomarkers indicative of adverse prostate cancer behavior—Gleason grade, tumor volume and detrimental molecular alterations—can be reproducibly detected in the urine of men with prostate cancer; Determine whether initial sampling of a panel of urine biomarkers and the repeated assessment of a urine biomarker panel over time will associate with the presence of significant versus insignificant cancer in the prostate, and thus can be used in informing decisions for continuing surveillance or proceeding with definitive treatment.

Specific Aims: 1) Determine if PCA3 and TMPRSS2:ERG mRNA concentrations in urine associate with the presence or development of clinically-significant prostate cancer using longitudinal repeat assessments in men on Active Surveillance; 2) Evaluate a panel of long non-coding RNAs (lncRNAs) in tissue and urine for the detection of significant prostate cancer in men on Active Surveillance; 3) Define and evaluate a panel of Gleason Pattern-associated RNAs in tissue and urine for the detection of significant prostate cancer in men on Active Surveillance.

Role: Co-Investigator

Contact information at Funding Agency: Alexander Moreno, amoreno@fhcrc.org

Award No. N/A (MPIs: Maher/Feng/Sharifi/Tomlins) 01/01/15 - 12/31/16

0.12 cal

mos Prostate Cancer Foundation

Identifying Early Biomarkers of Anti-Androgen Treatment Resistance and Lethal Prostate Cancer

Goal(s): Radiation Therapy Oncology Group (RTOG) 96-01 represents a phase III trial of of salvage radiation therapy (RT) alone versus combined therapy (androgen deprivation therapy [ADT] and RT). This represents a highly unique population of 771 patients with aggressive localized prostate cancer following standard treatment options with long-term clinical outcomes (median follow-up of 9 years). The overarching goal of this proposal is to leverage this unique patient population to explore the molecular underpinnings predictive of treatment response and associated with lethal disease.

Role: Co-PI

Contact Information at funding agency: Audrey Gardner, PCF Applications (applications@pcf.org)

Award No. N/A (PI: Rubin/Tomlins)

07/31/15 - 07/31/17

0.12 cal mos

Prostate Cancer Foundation

Integrative Genomics of Prostate Cancer Progression

Goal(s): Retrospectively collect, review, and perform comprehensive molecular characterization on the original diagnostic biopsy or prostatectomy samples from men with castration resistant prostate cancer (CRPC) participating on the CRPC 500 trial to identify molecular determinants of prostate cancer progression.

Specific Aims: 1. Collect and histologically characterize original primary ADT-naïve specimens from patients enrolled in the CRPC 500 trial. 2. Determine the molecular landscape of multiple tumor foci from the original ADT-naïve CRPC 500 specimens through DNA and RNA sequencing. 3. Identify molecular mediators of PCa progression and track the progressing clone through an integrative molecular profiling analysis of paired primary ADT-naïve and CRPC specimens.

Contact Information at funding agency: Audrey Gardner, PCF Applications (applications@pcf.org)

Mosquera, Juan M.

CURRENT

U01 CA162148 (Garraway, L.)

Systemic Genetic Characterization of African American Prostate Cancer

0.6 calendar

National Institute of Health

Grants Officer: N/A

7/1/12-6/30/17

The over-arching goal of this proposal is to undertake a definitive somatic genetic and functional characterization of African-American prostate cancer.

Aim 1. Design and validation of hybrid capture-based genomic profiling protocol to genetically characterize African American prostate cancer tumor samples

Aim 2. Profiling of a cohort of African American prostate cancer samples

Aim 3. Functional and mechanistic studies of operant signaling pathways in African American cell lines in vitro

AACR SU2C Dream Team (Chinnaiyan, A. / Sawyers, C.)

Precision Therapy of Advanced Prostate Cancer

1.2 calendar

American Association for Cancer Research

Grants Officer:

7/1/12-7/31/16 (NCTX)

Project Goals: To examine the functional relevance of 5-10 candidate genes implicated by prostate cancer somatic mutations, develop companion functional approaches for the analysis of DNA and RNA sequencing and determine key targetable genes associated with prostate cancer.

Starr Foundation Grant, I7-A722 (Chen, Y. / Rubin / Carver, B. / Beltran, H.)

Co-clinical trials using organoids for patients with advanced prostate cancer

0.12 calendar

Starr Foundation Grant

Grants Officer: Sylvie LeBlanc; email: leblancs@mskcc.org; phone: 212-639-8489

1/1/14-12/31/15

This project will create organoid lines from advanced prostate cancer patients to generate mutational and copy number data of each organoid line, determine whether *in vitro* sensitivity can predict for patient response, and generate potential biomarkers.

Aim 1. Generate clinically well-annotated organoid lines that accurately recapitulate the clinical and molecular diversity of abiraterone-resistant CRPC and NEPC

Aim 2. Characterize the mutational profile and copy number profile of each organoid line

Aim 3. Determine the *in vitro* drug sensitivity profile of organoid lines and correlate with patient response

R01 CA184712 (Rubin, M / Lin, D.)

Precision Medicine Approach to Prostate Cancer Active Surveillance

1.8 calendar

National Institute of Health

Grants Officer: Sarah E. Scharf; email: sarah.scharf@nih.gov; phone: 240-276-5472

8/1/14-7/31/19

The goal of this project is to confirm a novel panel of tissue-based biomarkers to determine the presence of or

progression to aggressive disease in early stage PCa and prove that these biomarkers will reliably predict PCa progression and/or under-staging and grading

Aim 1. Confirm a novel panel of tissue-based biomarkers to determine the presence of or progression to aggressive disease.

Aim 2. Evaluate emerging tissue-based biomarkers for aggressive PCa in men on AS.

R01 CA179100 (Rickman)

Mechanistic Insights Underlying ERG-induced Taxane Resistance in Castration –Resistant Prostate Cancer

0.36 calendar

National Institute of Health

Grants officer: Sarah M. Lee; 240-276-6280; Sarah.Lee@nih.gov

04/11/14-02/28/19

Aim: To characterize the mechanism underlying ERG-induced taxane resistance in castrate resistant prostate cancer

U01 CA086402 (Thompson, I.)

Biomarkers and clinical parameters associated with Gleason score upgrading

1.2 calendar

National Institute of Health

Grants Officer: Chris Green; email: greenc@uthscsa.edu; phone: N/A

7/1/14-8/31/15

Project Goals: To grade and stage, tumor volume, presence of perineural and/or angiolymphatic invasion and margin status will also be recorded. Each individual tumor nodule will be mapped in prostatectomy specimens, and provided its own Gleason score and pathologic tumor (pT) stage.

W81XWH-14-1-0466 (Tomlins)

Clonal Evaluation of Prostate Cancer by ERG/SPINK1 Status to Improve Prognosis Prediction

United States Dept. of Defense

0.96 calendar

Grants Officer: Emily Tran; email: tranc@mail.nih.gov; Phone: 240-276-6324

Goal(s): Utilize ERG/SPINK1 status to assess the frequency of multiclonality in clinically relevant scenarios and to determine whether incorporating tumor clonality improves prognostic prediction.

Specific Aims: To develop QIBC to assist radiologists in evaluation of bladder GTV on multimodality images (MM-bladder tumors); To develop decision support systems to assist clinicians in staging and monitoring of treatment response of bladder cancer by using image biomarkers, pathological information and diagnostic test results, and immunohistochemical biomarkers; To evaluate the effects of QIBC and CDSS-T on clinicians' inter-observer variability, efficiency and accuracy in estimation of bladder GTV and tumor treatment response by observer studies; To evaluate the CDSS-S and CDSS-T as clinical decision support tools for estimation of tumor treatment response in pilot clinical studies.

ENDED since last submission:

National Institute of Health, U01 CA111275 (PI Rubin/Chinnaiyan)

Title: EDRN BDL: A Systems Biology Approach to the Development of Cancer

Amount per year:

Duration: 7/1/10-6/30/15

Effort: 5%

Grants Management Specialist: Wendy Briscoe, briscoew@mail.nih.gov, Phone: 301-496-3160,

Aim 1. Discovery of novel prostate cancer specific gene fusions. Specific Aim 2: Discovery of prostate cancer gene aberrations by integrating DNA and RNA sample profiles.

TRUE, Larry. D.

ACTIVE

2 P50 CA97186 (Nelson)

9/1/13-8/31/18

NIH

0.84

calendar *Pacific*

Northwest Cancer SPORE

Core B: Biospecimen Core

The Specimen Core provides part of the infrastructure support for Projects 1-4, as well as future pilot and developmental projects. It has been designed to meet the needs of these projects, plus serve as a stand-alone system of specimen collection, storage, distribution and related clinical/research information dissemination that is based on over two decades of experience.

Role: Dr. True will serve as the Pathologist and Co-Director of Core B.

Sponsor Contact: Peter Nelson, M.D., Fred Hutchinson Cancer Research Center (FHCRC), 1100 Fairview Avenue N., MS: J6-500, PO Box 19024, Seattle, WA 98109-1024, pnelson@fhcrc.org

R01 CA176844-01 (Vasioukhin)

05/01/13 - 03/31/18

0.72 calendar

NIH

The Hippo Pathway in Prostate Gland Homeostasis and Prostate Cancer

This project hypothesizes that biomarkers of disease aggressiveness and prognosis can be measured in early stage prostate cancer and that these biomarkers will aid not only in choosing the initial course of therapy but also in decision-making during AS (Active Surveillance). The project proposes to interrogate a large multi-institutional cohort of men undergoing AS to confirm a platform of tissue and urine-based biomarkers that will reliably predict prostate cancer progression and or under-staging and –grading, thus determining patients who may avoid radical treatment, concurrently identifying men who may benefit from early treatment rather than active surveillance.

Role: Co-I

Sponsor Contact: James Pendleton, Fred Hutchinson Cancer Research Center (FHCRC), 1100 Fairview Avenue N., PO Box 19024, Seattle, WA 98109-1024, jpendlet@fhcrc.org

W81XWH13-2-0070 (Scher)

9/30/13-9/26/16

DOD

Toward the Practice of Precision Medicine: Multicenter validation of Biomarker Assays for Clinical Management of Prostate Cancer

UW Subaward:

1.8 calendar

The goal of this proposal is to revolutionize the clinical management of prostate cancer by cross-validating assays of integral biomarkers for prostate cancer that can be used in prospective, biomarker-driven clinical trials. This will be accomplished by facilitating critical collaboration between multidisciplinary teams of investigators at multiple institutions in order to 1) develop a pipeline of biomarkers prioritized for assay development, 2) determine the appropriate platform(s) for analysis, and 3) systematically address the preanalytical, analytical, and post-analytical variables including data redaction to validate and conduct tissue based assays in a CLIA environment.

Role: Co-I

Sponsor Contact: CDMRP, PCR, (301) 619-7079, cdmpr.pa@amedd.army.mil

Parent Institution: Memorial Sloan-Kettering Cancer Center; Award Administrator: Michael McGregor, mgregom@mskcc.org

P01 CA163227 (Balk)

5/1/13-4/30/18

0.696 calendar

NIH

Androgen Receptor Action In Castration Resistant Prostate Cancer

Core C: Biospecimen Core

The major goal of the Biospecimen Core is to provide a well-organized and standardized system of specimen collection, storage, distribution and related clinical/research information dissemination that is based on over two decades of experience. The Core will ensure consistency and quality assurance in the pathological analysis of tissue specimens. It will maintain a large series of prostate cancer xenograft lines developed by Core investigators, which will be used for proposed studies by the P01 investigators.

Role: Co-I

Sponsor Contact: Julienne Carty, Harvard University, 330 Brookline Ave. E/CLS 650, Boston, MA 02215, 617-735-2002, jcarty@bidmc.harvard.edu

PC 130652 (Tomlins)

9/30/14-9/29/17

0.936 calendar DOD

Clonal evaluation of prostate cancer by ERG/SPINK1 status to improve prognosis prediction

The objectives will be to retrospectively and prospectively identify cases for cohorts 1-3. Dr. True will be responsible for performing and evaluating ERG/SPINK1 dual IHC stains on 300 cases. He will also be responsible for transferring the remaining cases/sections to Dr. Tomlins at UMHS and evaluating ERG/SPINK1 dual IHC stains on 100 cases stained at UMHS. He will also work with co-investigators at UMHS and Cornell in study design, data analysis and interpretation, and in manuscript preparation.

Role: Co-Investigator

Sponsor Contact: CDMRP, (301)682-5507, help@cdmrp.org

Parent Institution: University of Michigan

NEW: W81XWH1410595 (Lin)

9/30/14-9/29/17

1.2 calendar

DOD

Biomarkers for Early Detection of Clinically Relevant Prostate Cancer: a Multi-Institutional Validation Trial

Dr. True will be responsible for reviewing slides of prostate needle biopsies and characterizing the prognostic pathologic parameters in biopsies of participants in the PASS study. He will also identify areas of cancer for tissue samples used in Aim 1 of the project.

Role: Co-Investigator

Sponsor Contact: CDMRP, (301)682-5507, help@cdmrp.org

Parent Institution: Fred Hutchinson Cancer Research Center

NEW: W81XWH-15-1-0430 (Nelson)

7/1/15-6/30/18

2% effort

DOD

Minimally-Invasive Assessments of Prostate Cancer Molecular Heterogeneity to Direct Precision Therapy

Dr. True will assist in the acquisition and assessment of tumors acquired from men with advanced prostate cancer, evaluate tumor purity, and assist with evaluations of tumor heterogeneity by histology and immunohistochemical methods.

Role: Co-Investigator

Sponsor Contact: CDMRP, (301)682-5507, help@cdmrp.org

Parent Institution: Fred Hutchinson Cancer Research Center

DOD

Prostate Cancer Biorepository Network

Dr. True participates in The Prostate Cancer Biorepository Network (PCBN). The goal of PCBN is to maintain and expand the current biorepository with high quality, well-annotated specimens that meet the critical needs of the prostate cancer research community, and which are obtained using optimized and standardized protocols.

Role: Co-Investigator

Sponsor Contact: CDMRP, (301)682-5507, help@cdmrp.org

ENDED SINCE LAST SUBMISSION:*Early Detection Research Network: Biomarker Developmental Laboratories*

9/22/10 – 6/30/15

NIH (2U01CA111244-06) Liu, A., PI

(DC/IDC whole period for all entries)

0.24 calendar

This is the continuation of our participation in The Early Detection Research Network (EDRN) with the goal that our gene expression findings in prostate cancer and bladder cancer can be translated into practical clinical tests for timely cancer detection and risk assessment (disease stratification). Our work continues to analyze prostate and bladder cancer molecular and cellular signatures that include secreted and cell surface proteins found in voided urine. We measure these proteins by proteomics technologies, mass spectrometry, or ELISA to derive a viable urine test that can be developed for detecting these urologic cancers.

Sponsor Contact: Jacob Kagan, Ph.D., Division of Cancer Prevention, NCI, NIH, 6130 Executive Boulevard, EPN Rom 3147, MSC 7362, Rockville, MD 20852-73642, kaganj@mail.nih.gov

Role: Co-I

Mechanisms and Markers of Prostate Cancer Metastases 7/1/09-7/31/14

1.8 calendar

NIH (2 P01 CA085859) Vessella, R., PI

The major goal of this award is to continue studies on prostate cancer (CaP) metastasis, especially focusing on the dissemination and growth of CaP in bone. This effort has coordinated much previous work from a variety of sources within the UW and is multi-disciplinary, incorporating cancer and bone biology, cancer endocrinology, pathology and genomics. Institutional partners include the FHCRC and the UW Institute of Stem Cell Sciences.

Core A: Tissues/Sera/Models

The major function of this core is to provide infrastructure support as follows: 1) Specimen acquisition, processing, storage and accession, 2) RT-PCR Immunohistochemistry and in situ hybridization services, 3) PSA and other immunoassay services, 4) tissue culture services, 5) CaP and control xenograft maintenance plus perform all xenograft studies.

Sponsor Contact: Suresh Mohla, Ph.D., Chief, Tumor Biology and Metastasis Branch, Division of Cancer Biology, NCI, NIH, Executive Plaza North, Room 5038, Rockville, MD 20852-7364, mohlas@mail.nih.gov

Role: Co-I