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TITLE: Intratumoral Heterogeneity of Aggressive Molecular Biomarkers in Lethal Primary Prostate Cancer

PRINCIPAL INVESTIGATOR: Aaron M. Udager, M.D., Ph.D.

CONTRACTING ORGANIZATION: University of Michigan

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Aaron M. Udager, M.D., Ph.D.

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5d. PROJECT NUMBER

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

Regents of the University of
Michigan
3003 S. State Street
Ann Arbor, MI 48109

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Over the past fifteen years, our understanding of the biology of prostate cancer has increased dramatically, and a number of specific genetic changes (i.e., biomarkers) have been identified that help us predict which patients with die from prostate cancer. At the same time, however, other research has shown that these genetic changes can vary significantly within a single tumor – a concept known as intratumoral heterogeneity – and the possibility of intratumoral biomarker heterogeneity represents a significant challenge to our ability to predict which patients will die from prostate cancer. In this study, we hypothesize that tumors in patients who eventually die from prostate cancer show increased intratumoral biomarker heterogeneity that is associated with other types of genetic changes. To examine this hypothesis, we are in the process of assessing how frequently specific biomarkers show intratumoral heterogeneity in these tumors and identifying the types of corresponding genetic changes.

15. SUBJECT TERMS

Prostate cancer, lethal disease, radical prostatectomy, molecular biomarkers, intratumoral heterogeneity, next-generation sequencing, ERG, SPINK1, PTEN, SChLAP1

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1. INTRODUCTION

Although most patients with prostate cancer will be cured by surgery and/or radiation, a small group of patients will develop metastases and, ultimately, die of prostate cancer. If we could identify patients early who will eventually die of prostate cancer, it is possible that they could receive additional treatments that would save their lives. Over the past fifteen years, our understanding of the biology of prostate cancer has increased dramatically, and a number of specific genetic changes (i.e., biomarkers) have been identified that help us predict which patients with die from prostate cancer. At the same time, however, other research has shown that these genetic changes can vary significantly within a single tumor – a concept known as intratumoral heterogeneity – and the possibility of intratumoral biomarker heterogeneity represents a significant challenge to our ability to predict which patients will die from prostate cancer. In this study, we hypothesize that tumors in patients who eventually die from prostate cancer show increased intratumoral biomarker heterogeneity that is associated with other types of genetic changes. To examine this hypothesis, we will assess how frequently specific biomarkers show intratumoral heterogeneity in these tumors and identify the types of corresponding genetic changes.

2. KEYWORDS

Prostate cancer, lethal disease, radical prostatectomy, molecular biomarkers, intratumoral heterogeneity, next-generation sequencing, ERG, SPINK1, PTEN, SChLAP1

3. ACCOMPLISHMENTS

What were the major goals of the project?

Aim 1. Determine the incidence and pattern of spatial intratumoral heterogeneity of aggressive molecular biomarkers in lethal primary prostate cancer.

Aim 2. Compare the frequency and spectrum of genomic alterations across spatially-distinct areas of lethal prostate cancer with intratumoral biomarker heterogeneity.

Aim 3. Evaluate transcriptomic alterations that accompany intratumoral biomarker heterogeneity in lethal prostate cancer.

What was accomplished under these goals?

Aim 1. Determine the incidence and pattern of spatial intratumoral heterogeneity of aggressive molecular biomarkers in lethal primary prostate cancer.

Obtain local IRB approval (months 1-2)

Study approval from the local Institutional Review Board (IRB) was obtained in Year 1 (task 100% complete).

Obtain HRPO approval (months 3-4)

Study approval from the Department of Defense Human Research Protection Office (HRPO) was obtained in Year 1 (task 100% complete).

Retrospectively identify radical prostatectomy specimens (n = 100) (months 5-6)

Prospectively maintained prostate cancer radical prostatectomy clinical databases were queried, and 100 study specimens were retrospectively identified in Year 1. However, hematoxylin and eosin (H&E) slides and/or formalin-fixed paraffin-embedded (FFPE) tissue blocks for many cases were missing from the pathology archive, and additional study specimens have been identified as replacements (task 100% complete).

Review slides from retrospectively identified specimens and select tissue for analysis (n = 200) (months 7-9)

Available H&E slides for study specimens were retrieved from the pathology archive, and Dr. Udager reviewed these specimens to select FFPE tissue for analysis. However, FFPE tissue blocks for many cases were missing from the pathology archive, and Dr. Udager has begun to review additional identified study specimens to select tissue for analysis (task approximately 50% complete).

Perform ERG/PTEN immunohistochemistry (n = 200) (months 10-21)

Nothing to report.

Perform ERG/SPINK1 immunohistochemistry (n = 200) (months 10-21)

ERG/SPINK1 immunohistochemistry (IHC) was performed on 100 FFPE tissue sections from 50 study specimens (task approximately 50% complete).

Perform SChLAP1 RNA in situ hybridization (n = 200) (months 10-21)

Nothing to report.

Analyze immunohistochemistry and RNA in situ hybridization results (n = 600) (months 13-24)

Dr. Udager reviewed 100 ERG/SPINK1 IHC slides from 50 study specimens. 31 tumors had an ERG+ component, and 26 tumors had an ERG- component – including 9 with

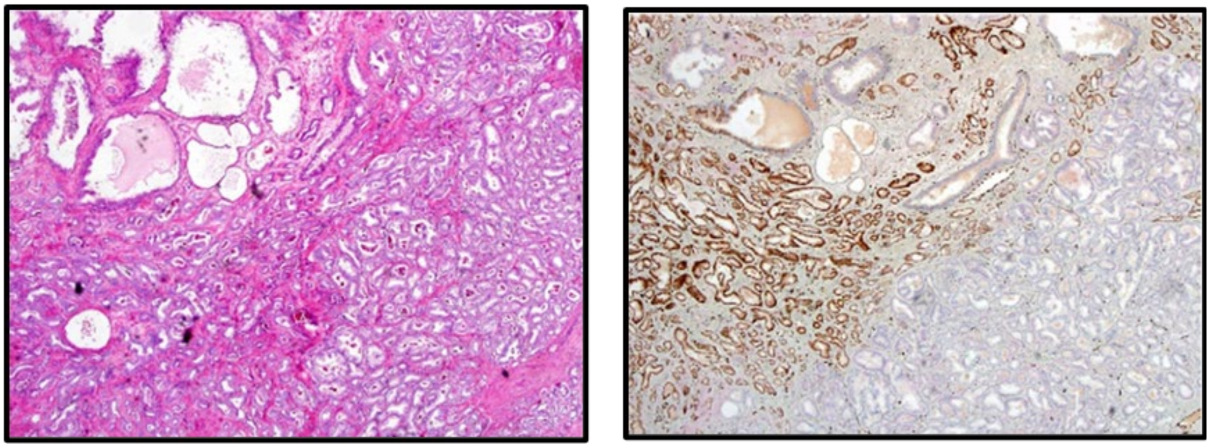

Figure 1. ERG/SPINK1 IHC highlights multiclonality in a subset of prostate cancer tumor nodules. (left) H&E and (right) ERG/SPINK1 IHC images of a prostate cancer tumor nodule from a radical prostatectomy specimen. The H&E image demonstrates a spatially contiguous focus of prostate cancer, while ERG/SPINK1 IHC reveals the presence of spatially coincident ERG-positive and ERG-negative prostate cancer clones in this tumor nodule.

SPINK1 overexpression; 7 tumors were comprised of distinct ERG+ and ERG- tumor components (**see Figure 1**; task approximately 17% complete).

<u>Aim 2. Compare the frequency and spectrum of genomic alterations across spatially-distinct areas of lethal prostate cancer with intratumoral biomarker heterogeneity.</u>

Select tissue areas for multiregion molecular profiling (n = 400) (months 13-24)

Nothing to report.

Extract DNA from tissue samples (n = 400) (months 21-28)

Nothing to report.

Profile extracted DNA (n = 400) (months (25-42)

Nothing to report.

Analyze DNA sequencing data and identify somatic variants and copy number alterations (n = 400) (months 35-44)

Nothing to report.

Correlate DNA sequencing data with intratumoral immunohistochemistry and RNA in situ hybridization results (months 45-48)

Nothing to report.

Compare DNA sequencing data across primary lethal and non-lethal prostate cancer (45-48)

Nothing to report.

Aim 3. Evaluate transcriptomic alterations that accompany intratumoral biomarker heterogeneity in lethal prostate cancer.

Extract RNA from tissue samples (n = 400) (months 21-28)

Nothing to report.

Profile extracted RNA (n = 400) (months 25-42)

Nothing to report.

Analyze RNA sequencing data and derive prognostic gene expression scores (n = 400) (months 35-44)

Nothing to report.

Correlate RNA sequencing data with intratumoral immunohistochemistry and RNA in situ hybridization results (months 45-48)

Nothing to report.

Compare RNA sequencing data across primary lethal and non-lethal prostate cancer (months 45-48)

Nothing to report.

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

The project has provided a number of ongoing professional development opportunities for Dr. Aaron Udager (Principal Investigator), including: research and professional development meetings with Dr. Arul Chinnaiyan (Designated Mentor) and Scott Tomlins (Co-Investigator); attendance at monthly Michigan Medicine Precision Medicine Tumor Board; attendance and research presentation at monthly Michigan Prostate Specialized Program of Research Excellence (SPORE) meetings; and, participation in the University of Michigan Program for Education and Evaluation in Responsible Research and Scholarship (PEERRS).

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 reporting period, we plan to finish selecting FFPE tissue for analysis and complete ERG/SPINK1 IHC on the entire set of study specimens. Then we will perform ERG/PTEN immunohistochemistry and *SChLAP1* RNA in situ hybridization on the selected tissue and analyze the results in order to identify areas for multiregion molecular profiling. We will then begin to extract DNA and RNA from these tissue areas and utilize targeted next-generation DNA and RNA sequencing to profile genomic and transcriptomic alterations.

4. IMPACT

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

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS

Changes in approach and reasons for change

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

H&E slides and/or FFPE tissue blocks for many cases were missing from the pathology archive, and therefore, we had to re-query the prospectively maintained prostate cancer radical prostatectomy clinical databases to identify replacements. In addition, the processing of research requests from the pathology archive was slow due to personnel shortages caused by the COVID-19 pandemic.

Changes that had a significant impact on expenditures

Nothing to report.

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

Nothing to report.

6. 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.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Aaron Udager
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-8254-5404
Nearest Person Month Worked:	4
Contribution to Project:	Dr. Udager led all aspects of the study. In addition, he reviewed study cases, selected FFPE blocks for analysis, and analyzed ERG/SPINK1 IHC results.
Funding Support:	N/A

Name:	Javed Siddiqui
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest Person Month Worked:	1
Contribution to Project:	Mr. Siddiqui oversaw database queries to identify study cases and performed ERG/SPINK1 IHC.
Funding Support:	N/A

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 Appendices for updated Other Support documents for Drs. Udager, Mehra, Chinnaiyan, and Tomlins, as well as Mr. Siddiqui. New and ended support is indicated for each investigator.

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

Collaborative Awards

N/A

Quad Charts

N/A

9. APPENDICES

Updated Other Support for Dr. Aaron Udager
Updated Other Support for Dr. Rohit Mehra
Updated Other Support for Mr. Javed Siddiqui
Updated Other Support for Dr. Arul Chinnaiyan
Updated Other Support for Dr. Scott Tomlins

OTHER SUPPORT

UDAGER, AARON

CURRENT

W81XWH-19-1-0407 Udager (PI) 3.66 CM
Department of Defense Total award amount 9/2019-8/2023
Tom Winter
Grants Management Specialist
sidney.t.winter.civ@mail.mil
240-357-1590

Intratumoral heterogeneity of aggressive molecular biomarkers in lethal primary prostate cancer

Goal(s): The goal of this project is to utilize immunohistochemistry, in situ hybridization, and next-generation sequencing to establish the frequency and pattern of intratumoral biomarker heterogeneity in lethal prostate cancer and delineate the spectrum of associated molecular alterations in these spatially-distinct areas. Specific Aims: Aim 1. Determine the incidence and pattern of spatial intratumoral heterogeneity of aggressive molecular biomarkers in lethal primary prostate cancer. Aim 2. Compare the frequency and spectrum of genomic alterations across spatially-distinct areas of lethal prostate cancer with intratumoral biomarker heterogeneity. Aim 3. Evaluate transcriptomic alterations that accompany intratumoral biomarker heterogeneity in lethal prostate cancer.

W81XWH-20-1-0405 Alumkal (PI) 0.60 CM (YR3)
Department of Defense total award amount 9/2020-8/2023
Tom Winter
Grants Management Specialist
sidney.t.winter.civ@mail.mil
240-357-1590

Targeting LSD1 in Neuroendocrine Prostate Cancer

Goal(s): The objectives of this proposal are to clarify mechanisms by which LSD1 promotes NEPC phenotypes and the anti-tumor activity of LSD1 inhibition so we may develop a new treatment strategy for NEPC patients and identify key companion biomarkers that indicate suppression of LSD1's critical function. Specific Aims: Aim 1: Identify an LSD1 inhibitor gene response signature and determine mechanisms by which LSD1 blocks gene expression in NEPC. Aim 2: Treat NEPC tumors in vivo with LSD1 inhibition and determine effect on tumor growth and differentiation. Aim 3: Determine mechanisms by which the LSD1+8a splice variant functions in NEPC.
Role: Co-Investigator
****New Support****

R37 CA222829 Xu (PI) 0.12 CM
NIH/NCI 1/2019-12/2023
Jennifer Meininger
Grants Management Specialist
jennifer.meininger@mail.nih.gov
240-276-6330

Real time fine needle assessment of architectural heterogeneity in prostate cancer

Goal(s): The specific aims include: 1) examining label-free PCa aggressiveness assessments in ex vivo human tissues; and 2) examining contrast-enhanced PCa aggressiveness assessments in mouse models in vivo. Specific Aims: Aim 1. Test an all-optical fine needle PA probe for identifying aggressive PCa in biopsy cores. Aim 2. Practice and examine the PA pre-biopsy via simulated biopsy procedures with ex vivo human prostates. Aim 3.

Examine the correlation between the PA measurements and the pathology of the PCa via an observational human subjects study with 67 patients
Role: Co-Investigator

U01 CA232931 Hadjiyski/Alva (MPI) 0.24 CM
NIH/NCI 5/2019-4/2024
Jennifer Meininger
Grants Management Specialist
jennifer.meininger@mail.nih.gov
240-276-6330
Biomarker-based tools for treatment response decision support of bladder cancer
Goal(s): The goal of this project is to validate the effectiveness of CDSS-T as an aid to the radiologists and the oncologists in assessment of bladder cancer change as a result of treatment through pilot clinical trials. Specific Aims: Aim 1. To perform a preparatory clinical trial with the clinicians at UM, which will simulate the real prospective clinical trial. Aim 2. To deploy the QIBC and CDSS-T tools at the three collaborating clinical sites. Aim 3. To use the QIBC and CDSS-T tools at the three clinical sites in the pilot clinical trial. Aim 4. To compare the clinicians' performance results with and without the QIBC and CDSST tools in the pilot clinical trial.
Role: Co-Investigator

P50 CA186786 Chinnaiyan/Palapattu/Heath (MPI) 0.60 CM
NIH/NCI 9/2019-8/2024
Jennifer Meininger
Grants Management Specialist
jennifer.meininger@mail.nih.gov
240-276-6330
Michigan Prostate SPORE
Goal(s): 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: Targeting Metastatic Prostate Cancer Patients with Biallelic Loss of CDK12. Project 2: Integrating a Novel MiPS-Based Next-Generation Sequencing Urine Assay for the Early Detection of Unfavorable Risk Prostate Cancer. Project 3: Exploring Ablation of the Androgen Receptor as a Therapeutic Approach for Castration-Resistant Prostate Cancer. Project 4: Targeting LSD1 in Neuroendocrine Prostate Cancer.
Role: Co-Investigator (Projects 2 and 4)

R01 CA186786 Alumkal (PI) 0.60 CM (YR2-5)
NIH/NCI 9/2020-8/2025
Elizabeth Bui
Grants Management Specialist
mimi.bui@mail.nih.gov
240-276-5365
Targeting Prostate Cancer Lineage Plasticity with BET Bromodomain Inhibition
Goal(s): The goal of this project is to understand molecular mechanisms by which BET bromodomain proteins promote neuroendocrine prostate cancer progression so we can target those mechanisms. Specific Aims: Aim 1: Determine mechanisms by which E2F1 and BRD4 cooperate to promote expression of a t-NEPC lineage plasticity survival program. Aim 2: Treat t-NEPC patient tumors implanted in mice with BETi or BETd and measure anti-tumor activity and NEPC differentiation. Aim 3: Prevent castration-induced t-NEPC lineage switch with BETi or BETd using a patient tumor model of t-NEPC lineage switch implanted in mice.
Role: Co-Investigator
****New Support****

W81XWH-21-1-0238	Udager (PI)	1.20 CM
Department of Defense	total award amount	6/2021-5/2024

Tom Winter
Grants Management Specialist
sidney.t.winter.civ@mail.mil
240-357-1590

Integrative molecular profiling of whole urine in African-American men with aggressive prostate cancer

Goal(s): The goals of this project are: 1) evaluate the performance of a novel whole urine NGS assay for the detection of high-grade prostate cancer in African-American men; and, 2) validate and apply a high-throughput NGS genomic profiling method for whole urine to identify African-American men with aggressive prostate cancer. Specific Aims: Aim 1. Evaluate the performance of an established whole urine NGS assay for the detection of highgrade prostate cancer in African-American men. Aim 2. Validate a high-throughput NGS-based germline genomic profiling method for whole urine and determine its impact on the detection of high-grade prostate cancer in African-American men.

****New Support****

W81XWH-21-1-0663	Udager (PI)	0.9 CM
Department of Defense	Total award amount	9/2021-8/2022

Judi Sgambato
judi.a.sgambato.civ@mail.mil
301-619-7040

Targeting FOXA1-Mediated Epigenetic Reprogramming in Aggressive Salivary Gland Cancer

Goal(s): The goal of this proposed research is to characterize the FOXA1 cistrome in salivary duct carcinoma and determine the efficacy of the LSD1 inhibitor GSK2879552 for disrupting FOXA1-mediated epigenetic reprogramming and tumor growth in ex vivo organoid cultures. Specific Aims: Aim 1. Define the FOXA1 cistrome in salivary duct carcinoma. Aim 2. Determine molecular and cellular responses to LSD1 inhibition in salivary duct carcinoma.

****New Support****

PENDING

R21 (PAR-19-184)	Day (PI)	0.40 CM
NIH/NCI		12/2021-11/2023

Grant Information
grantsinfo@nih.gov
301-945-7573

Delineation of tumor, stromal and immune transcriptomes at the infiltrating interface of muscle invasive bladder cancer

Goal(s): To provide positive impact by identifying cellular and molecular signatures of distinct cellular populations driving invasive progression. These findings could then lead to examination of candidate gene networks that will serve as the basis for biological function, potential biomarker identification and new therapeutic targets that are needed for bladder cancer patients who have been diagnosed with or have relapsed with muscle invasive disease. Specific Aims: Specific aim 1. To determine the transcriptomic signature of tumor cells and adjacent stroma isolated from the invasive interface of MIBC. Aim 2: To determine the cellular and transcriptomic signature of infiltrating immune cells in the invasive microenvironment of human bladder cancer. Aim 3: To analyze transcriptomic signatures from tumor, stromal and immune populations to identify gene regulatory programs unique to the invasive micro-environment of MIBC.

Role: Co-Investigator

****New Support****

OVERLAP FOR ALL CURRENT AND PENDING GRANTS

None

PREVIOUS (ENDED WITHIN THE LAST 5 YEARS)

U01 CA179106 Hadjiyski (PI) 0.60 CM (YR4)
NIH/NCI 5/2014-4/2019
Jennifer Meininger
Grants Management Specialist
Jennifer.meininger@mail.nih.gov
240-276-6330
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: Aim 1. Develop a quantitative image analysis tool (QIBC) for bladder GTV estimation on multi- modality (MM) images. Aim 2. Develop a computer decision support system (CDSS-S) to assist clinicians in cancer staging. Aim 3. Develop a computer decision support system (CDSS-T) to assist clinicians in evaluation of the change in the tumor characteristics as a result of neoadjuvant treatment. Aim 4. Evaluate the effects of QIBC and CDSS-T on inter-clinician variability and efficiency in estimation of GTV and treatment response. Aim 5. Evaluate CDSS-S and CDSS-T as decision support tools in pilot clinical studies.
Role: Co-Investigator

W81XWH-14-1-0466 Tomlins (PI) 4.80 CM (YR3)
Department of Defense total award amount 9/2014-8/2017 Theresa Miller, PhD
Grants Management Specialist
theresa.j.miller.ctr@mail.mil
Clonal evaluation of prostate cancer by ERG/SPINK1 status to improve prognosis prediction
Goal(s): The goal of this project is to utilize ERG/SPINK1 status to assess the frequency of multiclonality in clinically relevant scenarios and determine whether incorporating tumor clonality improves prognostic prediction. Specific Aims: Aim 1. Assess the frequency of multiclonality in clinically important scenarios using dual ERG/SPINK1 IHC. Aim 2. Determine whether multiclonality assessment at biopsy improves prediction of pathology at prostatectomy. Aim 3. Assess whether multiclonality assessment of index foci at prostatectomy improves outcome prediction.
Role: Co-Investigator

OTHER SUPPORT

MEHRA, ROHIT

CURRENT:

1U01CA214170-01 (PI: Chinnaiyan) 09/15/16 – 08/31/22 0.48 Calendar MO
NIH/NCI Source Country: USA
Annual Direct: Total Award:
The Early Detection Research Network (EDRN): Biomarker Developmental Laboratories (U01)
Discovery and qualification of transcriptomic biomarkers for the early detection of aggressive prostate cancer
Goal(s): 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.
Specific Aim(s): 1) Identify novel aggressive prostate cancer-associated transcriptomic biomarkers nominated from our MiTranscriptome analysis; 2) Develop transcriptomic tissue biomarkers of aggressive prostate cancer; 3) Develop non-invasive urine transcriptomic biomarkers of aggressive prostate cancer
Contact Information at funding agency: Kagan, Jacob; jk308z@nih.gov
Role: Co-Investigator
Overlap: None

2 P50 CA186786-06 (MPIs: Chinnaiyan, Heath/Palapattu)09/03/19 – 08/31/24 .30 Calendar MO
NCI/NIH Source Country: USA
Annual Direct: Total Award:
Michigan Prostate SPORE
Goal(s): 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: The specific aims of the Tissue Core are 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; 4) 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.
Program Official: Julia Arnold, jarnold@mail.nih.gov, 240-276-591
Role: Co-Investigator of Tissue Core C
Overlap: None

W81XWH1910424 09/01/2019 – 08/31/2022 0.30 Calendar MO
DOD (PI: Pitchiaya) Source Country: USA
Annual Direct: Total Award:
Unraveling tumor microenvironment heterogeneity in advanced prostate cancer
Goal(s): To understand the impact of tumor microenvironment heterogeneity, especially among immune infiltrates, cancer-associated fibroblasts and tumor vasculature, in the progression of advanced prostate cancer.
Specific Aim(s): (1) Investigate the evolution of tumor microenvironment during PCa progression. (2) Understand the impact of therapeutic intervention on tumor microenvironment. (3) Create a human prostate tumor cell atlas to stratify aggressive PCa subtypes in the general and veteran population.

Grants Specialist: Thomas Winter, Sidney.t.winter.civ@mail.mil, 240-357-1590
Role: Co-I
Overlap: None

W81XWH-19-10407 09/01/2019 – 08/31/2023 0.60 Calendar MO
DOD (PI: Udager) Source Country: USA
Annual Direct: Total Award:
Intratumoral heterogeneity of aggressive molecular biomarkers in lethal primary prostate cancer
Goal(s): The goal of this project is to utilize immunohistochemistry, in situ hybridization, and next-generation sequencing to establish the frequency and pattern of intratumoral biomarker heterogeneity in lethal prostate cancer and delineate the spectrum of associated molecular alterations in these spatially-distinct areas.
Sepcific Aim(s): (1) Determine the incidence and pattern of spatial intratumoral heterogeneity of aggressive molecular biomarkers in lethal primary prostate cancer. (2) Compare the frequency and spectrum of genomic alterations across spatially-distinct areas of lethal prostate cancer with intratumoral biomarker heterogeneity. (3) Evaluate transcriptomic alterations that accompany intratumoral biomarker heterogeneity in lethal prostate cancer.
Grants Specialist: Thomas Winter, Sidney.t.winter.civ@mail.mil, 240-357-1590
Role: Co-I
Overlap: None

1 R01 CA240991-01 09/01/2019 – 08/31/2025 0.36 Calendar MO
NCI/NIH (PI: Morgan/Spratt) Source Country: USA
Annual Direct: Total Award:
Determining the clinical impact of gene expression testing in localized prostate cancer
Goal(s): The long-term goal of this project is to simultaneously decrease treatment-related morbidity from unnecessary over-treatment of men with localized prostate cancer (PCa) while curing more men by minimizing under-treatment of men with higher risk PCs.
Specific Aim(s): (1) Develop an integrated clinical-genomic risk stratification system designed to systematize interpretation of GEC testing. We hypothesize that by developing integrated clinical-genomic risk groups we can identify patients most appropriate for AS while maintaining a standard, category-driven framework. (2) Prospectively define the utility and safety of GEC testing to reduce overtreatment of men with newly diagnosed PCa. Through the statewide MUSIC and MROQC initiatives, we will conduct a large randomized trial of men with newly diagnosed favorable risk PCa. We hypothesize that GEC testing will decrease the use of primary therapy and increase QOL at 3 years, while maintaining rates of grade reclassification and biochemical recurrence at the same time point. (3) Determine the impact of GEC testing on treatment failure and patient-reported QOL in men at high risk of recurrence post-prostatectomy on the G-MINOR trial. The G-MINOR trial, randomizing 350 men at high risk of local failure after prostatectomy to clinicopathologic risk stratification +/- GEC testing, completed accrual in June 2018 to assess decision making based on use of a GEC. We hypothesize that use of a GEC in higher risk patients will provide more accurate risk stratification and targeted treatment decisions, leading to improved cancer control and QOL without increasing overall rates of adjuvant radiotherapy.
Program Official: Erica Breslau, breslaue@mail.nih.gov
Role: Co-I
Overlap: None

5 P01 CA093900-15 07/02/20 - 05/31/25 0.90 Calendar MO
NCI/NIH (PI: Keller) Source Country: USA
Annual Direct: Total Award:
The Biology of Prostate Cancer Skeletal Metastases: Core C (Bone Core)

Goal(s): The ultimate goal is to define the cellular and molecular mechanisms that surround PCa skeletal metastases to facilitate translation into clinical application. The Bone Core of the Program Project will provide shared facilities and services for processing and interpretation of tissues from the animal models utilized in all projects of the program. The overall goal of the core facility is to provide centralized histologic and image analysis support for investigators in the project. Such a standardized format with provide valuable information and consistency across the projects in the program.
Specific Aim(s): (1) Experimental design/consultation. This include methods regarding endpoint analyses and abilities and limitations of methods. (2) Pathological interpretation. For histologic specimens, histopathology and scoring of immunohistochemistry. (3) Processing of tissues. Both osseous tissues and pooling resources for soft tissue processing. This includes fixation, decalcification, paraffin embedding and sectioning of decalcified sections and fixation, plastic embedding and sectioning of undecalcified sections. (4) Routine and special stains for mineralized tissues. This includes for mineralized tissues, osteoclasts and immunohistochemistry. (5) Histomorphometric analysis of both osseous sections and tumor tissue. This includes measurement of specific bone-related structural and cellular parameters. (6) Procurement of clinical tissue samples. Bone marrow samples for disseminated tumor cells isolation and blood for circulating tumor cells and serum as needed.
Role: Pathologist
Program Official: Joanna Watson, watsonjo@mail.nih.gov, 240-276-6230
Overlap: None

W81XWH-20-KCRP-IDA (Cieslik) 09/01/21 – 08/31/23 0.60 CM
DOD, KC200243 Source Country: USA
Annual Direct: yr Total Award:
Phased genomics for improved non-invasive diagnosis and risk stratification of kidney cancers based on genomic instability and associated CpG hypermethylation
Goal(s): The overarching goal of the project is to develop novel non-invasive biomarkers for kidney cancer
Specific Aim(s): Aim 1: To systematically examine the association between whole-genome doubling, chromosomal instability, and hypermethylation across the biological and clinical spectrum of renal cell carcinomas. Aim 2: To develop and validate quantitative measures of chromosomal instability as an early prognostic biomarker in renal cell carcinomas. Aim 3: To assess the clinical feasibility and utility of quantitative CIN for the prognostic stratification and non-invasive diagnosis of high-risk ccRCC.
Contact Information at funding agency: TBD
Role: Co-Investigator
Overlap: None
****New Support****

W81XWH-21-2-0024 (Vaishampayan) 09/15/21 – 08/31/22 0.60 CM
DOD Source Country: USA
Annual Direct: yr Total Award:
University of Michigan Phase I/II Assessment in Kidney Cancer Therapeutics: (UMPAKT)
Goal(s): To create a kidney cancer focused early therapeutics team within the multi-tumor experimental therapeutics (MET) program at the University of Michigan.
Specific Aim(s): (1) To meet the metrics required as a clinical trial site within the Kidney Cancer Research Consortium (KCRC). (2) Discovery of novel targets and translational biomarkers that will enable selection of individualized therapies towards developing a personalized approach to kidney cancer management.
Contact Information at funding agency: TBD
Role: Co-Investigator
Overlap: None
****New Support****

PENDING:

21-PAF09144 (Alumkal) 10/01/21 – 09/30/2024 0.60 CM
Astellas Pharma to NCCN Source Country: USA
Annual Direct: yr Total Award:
Clarifying Tumor and Microenvironmental Determinants of Enzalutamide Resistance
Goal(s): The goal of this proposal is to understand whether differences in the tumor architecture or tumor microenvironment are associated with the risk of NEPC development and resistance to enza treatment. Clarifying these determinants is predicted to lead to better stratification of patients at greatest risk of NEPC development so we may develop co-targeting strategies.
Contact Information at funding agency: TBD
Role: Co-Investigator
Overlap: None

22-PAF00568 (Chinnaiyan, Tosian) 7/1/2022 – 06/30/2027 0.60 CM
NIH Source Country: USA
Annual Direct: yr Total Award:
Michigan-VUMC Biomarker Characterization Center
This application proposes the formation of the Michigan-Vanderbilt University Medical Center (VUMC) EDRN Biomarker Characterization Center (BCC). This BCC represents a collaborative, multi-disciplinary team of academic (University of Michigan (U-M) and VUMC) and industry (LynxDx) partners focused on discovering, developing, and scaling clinical-grade assays for the early detection of aggressive prostate cancer.
Contact Information at funding agency: TBD
Role: Co-Investigator
Overlap: None

PREVIOUS:

W81XWH-16-1-0314 (PI: Mehra) 07/01/16 – 6/30/19 1.2 CM
Department of Defense Idea Award Source Country: USA
Annual Direct: yr Total Award:
Discovery and characterization of PRCAT47: A novel prostate lineage and cancer specific long non-coding RNA (PC150246)
Specific Aims and Goal(s): 1) To elucidate the molecular mechanism behind PRCAT47 function 2) To assess clinical utility of PRCAT47 as a prognostic or diagnostic biomarker 3) To interrogate the therapeutic potential of PRCAT47 using clinical grade antisense oligos (ASOs).
Contact Information at funding agency: Juan A. Rodriguez, Phone: 301-619-2367; Email: juan.a.rodriguez236.civ@mail.mil

P01-CA093900 (PI: Keller) 06/17/15 – 05/31/20 0.9 CM
NIH Source Country: USA
Annual Direct: yr Total Award:
The Biology of Prostate Cancer Skeletal Metastases
Goal(s): The ultimate goal is to define the cellular and molecular mechanisms that surround PCa skeletal metastases to facilitate translation into clinical application
Specific Aim(s): 1. Provide a highly interactive research program to allow cross-fertilization of ideas among Program investigators; 2. Provide resources and expertise needed to assist investigators in achieving their

research goals; 3. Manage administrative aspects of the program to ensure proper management of resources, equity in use of Cores and troubleshoot any issues that may arise; 4. Seek new collaborative opportunities within and outside of the Program
Contact Information at funding agency: Grants Management Specialist: Jennifer S. Meininger, Email: Jennifer.meininger@nih.gov Phone: (240) 276-6330
Role: Pathologist of Core 3 (Bone Core)

W81XH1520018 (PI: Scher/Hussain) 06/15/15 – 06/14/18 0.12 CM
Sloan Kettering Institue for Cancer Research (DOD Prime) Source Country: USA
Annual Direct: yr Total Award:
PCCTC Affiliate Clinical Research Sites - The University of Michigan Site

Aims and Goal(s): The objective of this RFA is to solicit applications for PCCTC Affiliate Clinical Research Site membership. Affiliate Clinical Research Site participation is intended to enrich the Consortium's research areas which include but are not limited to: Clinical development opportunities based on the strength of the underlying science, particularly the biologically-based translational science of its members. Informative, sequential trial development with individual trials incorporating A) outcome measures corresponding to the unmet needs associated with the specific clinical state of the disease for which the drug is being tested and B) biomarkers tailored to the compound's mechanism of action. Investigator-initiated trials that optimize dose, explore novel combinations, and lead to the discovery and validation of predictive biomarkers of sensitivity that can guide the use of an investigational product.
Contact Information at funding agency: Annmarie Pacchia, 646-227-3273, sponsorp@mskcc.org
Role: Co-Investigator
Overlap: None

P50 CA69568 (PI: Chinnaiyan) 09/11/14 - 08/31/19 0.3 CM
NCI Source Country: USA
Annual Direct: yr Total Costs:
SPORE in Prostate Cancer
Goal(s): 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. The specific aims of the Tissue Core are 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; 4) 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.
Contact Information at funding agency: Jennifer S. Meininger, 240-276-6330, jennifer.meininger@nih.gov
Role: Co-Investigator of Tissue Core

(PI: Morgan) 07/01/15 – 06/30/17 0.6 CM
National Comprehensive Cancer Network Source Country: USA
Salary support: yr Total award: yr
Tissue-based genomics for risk stratification in localized renal cell carcinoma
Goal(s): The goal of the proposed research is to develop a molecular diagnostic tool that may facilitate the identification of clinically indolent small renal masses that may be preferentially managed by active surveillance.
Specific Aim(s): (1) Identify the expression of cell cycle proliferation genes within surgically resected renal tumors that predict recurrence and cancer-specific mortality following radical nephrectomy. (2) Determine the correlation between gene expression profile scores generated from biopsies and from corresponding surgical specimens in patients with paired biopsy and nephrectomy tissue. (3) Delineate the association

between renal mass biopsy gene expression profile scores and observed tumor growth rate in patients with RCC managed by active surveillance.
Contact Information at funding agency: FoundationProposals@nccnfoundation.org
Role: Co-Investigator

U01CA183027 (PIs: Chinnaiyan, Linehan) 02/12/14 - 01/31/17 0.6 CM
NIH Source Country: USA
Annual Direct: yr Total Award:
Integrative molecular imaging and sequencing of prostate cancer
Goal(s): To better understand what makes some prostate cancers aggressive and others indolent by combining advanced MRI and metabolic imaging with genomic sequencing.
Specific Aim(s): (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.
Contact Information at funding agency: Henderson, Lori A., hendersonlori@mail.nih.gov, 240.276.5930
Role: Co-Investigator

PC121111 (PI: Scher, H.) 09/30/13 – 09/29/16 0.9 CM
Department of Defense Source Country: USA
Annual Direct: yr Total Award:
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 TMPRSS2:ERG assays; Validate the utility of the TMPRSS2:ERG TMA assay for the noninvasive 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 Aim(s): (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.
Contact Information at Funding Agency: Kathy E. Robinson, Grants Officer, Us Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick Md 21702-5014
Role: Co-Investigator

1UM1HG006508-01A1 (PI: Chinnaiyan) 07/19/13 – 05/31/17 0.6 CM
National Institutes of Health Source Country: USA
Annual Direct: yr (Project 2) Total Award:
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 Aim(s): 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.
Contact Information at funding agency: Harvey, Zephaun, harveyz@mail.nih.gov, 301 435-7859
Role: Co-Investigator

701640 (PI: Palapattu) 09/01/15 – 09/01/17 0.6 CM
Prostate Cancer Foundation Source Country: USA Salary support: yr Total Award: yr
Testing Targeted NK (TaNK) cell Therapy in Prostate Cancer
Specific Aims and Goal(s): (1) Test and evaluate NK-92 PSMA expressing CAR cells in pre-clinical models of prostate cancer. (2) Interrogate NK-92 PSMA expressing CAR cell function and response in the context of ADT. (3) Perform a first in man phase I neoadjuvant NK-92 PSMA expressing CAR cell clinical trial in men with high risk prostate cancer.
Contact Information at funding agency: Dr. Howard Soule, applications@pcf.org, Prostate Cancer Foundation, 1250 4th Street, Santa Monica, CA 90401
Role: Co-Investigator

Prostate Cancer Foundation (PI: Mehra) 05/20/13 - 05/20/16 1.2 CM
Young Investigator Award Source Country: USA
yr Total Award:
Clinico-pathological characterization of novel lncRNAs in prostate cancer risk stratification
Goal(s): This proposal aims to elucidate the clinicopathological associations and molecular basis for SChLAP1, a novel prostate cancer long non-coding RNA, and to assess the suitability of a SChLAP1 in situ hybridization assay for clinical translation for the detection of high-risk prostate cancers.
Specific Aim(s): To evaluate the association of SChLAP-1 with prostate cancer patient outcomes and lethal androgen independent metastatic prostate cancer; to characterize SChLAP1 expression in multifocal localized prostatic adenocarcinoma, and select histologic variants of prostate cancer including aggressive variants; to determine the relationship between SChLAP1 with androgen receptor signaling and TMPRSS2-ETS prostate cancer gene fusions; to elucidate mechanisms of SChLAP1 function in driving prostate cancer aggressiveness.
Contact Information at funding agency: Dr. Howard Soule, applications@pcf.org, Prostate Cancer Foundation, 1250 4th Street, Santa Monica, CA 90401

OTHER SUPPORT

SIDDIQUI, JAVED

CURRENT

U01 CA214170 09/15/16 – 08/31/21 2.4 CM
NIH/NCI (PI: Chinnaiyan) yr
The Early Detection Research Network: Biomarker Developmental Laboratories (U01) Discovery and qualification of transcriptomic biomarkers for the early detection of aggressive prostate cancer
Goal(s): 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.
Specific Aim(s): 1) Identify novel aggressive prostate cancer-associated transcriptomic biomarkers nominated from our MiTranscriptome analysis; 2) Develop transcriptomic tissue biomarkers of aggressive prostate cancer; 3) Develop non-invasive urine transcriptomic biomarkers of aggressive prostate cancer
Contact Information at funding agency: Kagan, Jacob; jk308z@nih.gov
Role: Technical Director

W81XWH-19-1-0407 09/01/19 - 08/31/23 1.2 CM
DOD (PI: Udager) yr
Intratumoral heterogeneity of aggressive molecular biomarkers in lethal primary prostate cancer
Goal: 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.
Goal(s): The goal of this project is to utilize immunohistochemistry, in situ hybridization, and next-generation sequencing to establish the frequency and pattern of intratumoral biomarker heterogeneity in lethal prostate cancer and delineate the spectrum of associated molecular alterations in these spatially-distinct areas.
Contact Information at funding agency: Tom Winter, 240-357-1590, Sidney.t.winter.civ@mail.mil
Role: Co-Investigator

P50 CA186786 09/11/14 - 08/31/24 0.6 CM
NIH/NCI (PI: Chinnaiyan, Palapattu, Heath) yr
Michigan Prostate SPORE
Goal: 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 Aim(s): 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.
Contact Information at funding agency: Jennifer S. Meininger, 240-276-6330, jennifer.meininger@nih.gov
Role: Technical Director of Tissue Core

R35 CA231996 9/1/18 – 8/31/25
NIH/NCI (PI: Chinnaiyan) yr
Exploring Precision Oncology: From Gene Fusions to lncRNAs
Goal(s): advance the field of precision oncology by providing new community resources, identifying novel biomarkers, exploring the therapeutic targeting of nominated molecular players, and adding to the knowledge-base of cancer development mechanisms, particularly those of lncRNAs.
Specific Aims: 1). To examine the incremental specificity for high grade prostate cancer (i.e., Gleason 6+) of prostate MRI above and beyond PSA, PCA3 and TMPRSS2:ERG with the sensitivity held constant at 90% in the initial biopsy setting. 2) To evaluate the potential for novel laboratory biomarkers, including but not limited to urine RNA sequencing chip, tissue prints for methylation field effect to predict findings on MRI 3) To evaluate the role of radiomics to improve upon standard diagnostic MRI protocols for the diagnosis of high-

grade prostate cancer. 4) To evaluate how changes in laboratory biomarkers and prostate MRI over a two-year period predicts subsequent diagnosis of high-grade prostate cancer. 5) To expand the current EDRN's unique pre-diagnostic reference set with RNA sequencing of pre-biopsy urine. We will apply the uMIPS RNA sequencing chip on banked urine samples from the PCA3 cohort. This will be evaluated on those who underwent initial and repeat prostate biopsies. 6) To evaluate the potential for precancerous lesions to progress to invasive cancers over a two-year period.
Contact Information at funding agency: Tawnya McKee, mckeeta@mail.nih.gov, 240-276-5719
Role: Technical Director

PREVIOUS:

04/01/18-03/31/20
NIH
EDRN Prostate MRI Biomarker Study and Reference Set
Goals: The commercialization of magnetic resonance imaging (MRI) fusion biopsies has resulted in a dramatic increase in the use of MRI imaging for prostate cancer. How best to use MRI in the initial prostate biopsy setting given the availability of validated prostate cancer early detection markers is uncertain. Specific Aim(s): The primary aim of this study is to see if the addition of prostate MRI to a panel including PSA, PCA3, TMPRSS2: ERG will significantly improve specificity for high-grade prostate cancer by 10%. The subsequent exploratory aims will: 1) create an optimal panel of urine and blood biomarkers that will select those cases most likely to benefit from a MRI targeted biopsy, 2) directly compare PSA and urinary biomarkers with MRI to determine which ones are "value added" in the setting of initial biopsy, 3) evaluate changes in these biomarkers and MRI to determine if longitudinal changes predict subsequent high-grade prostate cancer, 4) improve diagnostic MRI acquisitions to yield increased test performance, and 5) be the first study to make a comprehensive comparison of multiple RNA based biomarkers at initial biopsy. Importantly, this study will create a unique, prospective, cohort that will become the foundational reference-set for future approaches aimed at optimizing the diagnostic performance of integrated imaging and biomarker(s) approaches.
Role: Research Area Specialist Lead

15CHAS07 (PI: Chinnaiyan) 10/01/15 – 03/12/20
Prostate Cancer Foundation yr
Prostate Cancer Foundation Dream Team Continuation of the CRPC 500 Cohort Study
Goal(s): 1) Continue to gather clinical follow-up on patients enrolled on the CRPC 500 cohort. This will fund the clinical coordination site to maintain data collection across the multi-institutional cohort. To help facilitate access of this data by the research community we will establish a "Data Sharing Core" to enable easy access and sharing of the sequence data along with valuable clinical parameters across the consortium. We will explore the use of commercial cloud based infrastructure to support this initiative. 2) Identify 150 patients out of 500 from the CRPC500 study who have progressed for re-biopsy and whole exome and transcriptome sequencing analysis. This will allow us to assess tumor evolution and decipher molecular mechanisms of resistance. Matched progression biopsies will markedly increase the statistical power to attribute causality to alterations identified. 3) Identify and sequence 150 CRPC patients that have progressed post-abiraterone and/or postenzalutamide. This will allow us to establish the molecular landscape of a post-Abi/post-Enza cohort of patients. Compare molecular and morphological alterations with the West Coast Dream Team. Contact Information at funding agency: Dr. Howard Soule, applications@pcf.org, Prostate Cancer Foundation, 1250 4th Street, Santa Monica, CA 90401
Role: Technical Director

CURRENT

R35CA231996 (PI: Chinnaiyan) 09/01/18 – 08/31/25 6.0 CM
National Institutes of Health Total Award:
Exploring Precision Oncology: From Gene Fusions to lncRNAs
Goal(s): advance the field of precision oncology by providing new community resources, identifying novel biomarkers, exploring the therapeutic targeting of nominated molecular players, and adding to the knowledge-base of cancer development mechanisms, particularly those of lncRNAs.
Specific Aims: None.
Contact Information at funding agency: Tawnya McKee, mckeeta@mail.nih.gov, 240-276-5719

U24CA210967 (MPIs: Chinnaiyan, Nesvishkii, Dhanasekaran) 09/15/16 – 08/31/21 0.6 CM
NIH Total Award:
University of Michigan Proteogenomics Data Analysis Center
Goal(s): to perform integrative analysis of data generated using the Clinical Proteomic Tumor Analysis Consortium (CPTAC). The Center at the University of Michigan is one of the four Centers funded by CPTAC. It will work, in coordination with other Centers, to analyze and integrate proteomics, genomics, and transcriptomics data generated for 3-4 cancer patient cohorts, ~ 100 samples in each cohort. The Center will generate data analysis reports to be shared with other members of the Consortium.
Specific Aim(s): 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.
Contact Information at funding agency: Rodriguez, Henry, rodriguezh@mail.nih.gov, 301 496-1550

1U01CA214170-01 (MPI: Chinnaiyan) 09/15/16 – 08/31/21 1.8 CM
NIH/NCI Total Award:
The Early Detection Research Network: Biomarker Developmental Laboratories (U01) *Discovery and qualification of transcriptomic biomarkers for the early detection of aggressive prostate cancer*
Goal(s): 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.
Specific Aim(s): 1) Identify novel aggressive prostate cancer-associated transcriptomic biomarkers nominated from our MiTranscriptome analysis; 2) Develop transcriptomic tissue biomarkers of aggressive prostate cancer; 3) Develop non-invasive urine transcriptomic biomarkers of aggressive prostate cancer
Contact Information at funding agency: Kagan, Jacob; jk308z@nih.gov

1 R01 CA200660-01A1 (PIs: Grembecka, Chinnaiyan) 08/01/16 - 07/31/21 0.48 CM
NIH/NCI Total Award:
Targeting the MLL complex in Castration Resistant Prostate Cancer

Goal(s): to develop new therapy for castration resistant prostate cancer patients by blocking the menin-MLL interaction.

Specific Aim(s): 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.

Contact Information at funding agency: Elesinmogun, Funmi, elesinmf@mail.nih.gov, (240) 276-6313

P50 186786 (PI: Chinnaiyan, Palapattu, Heath))	09/11/14 - 08/31/24	2.4 CM
NIH/NCI	Total Award:	

Michigan Prostate SPORE

Goal(s): 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.

Overall: Michigan Prostate SPORE

Specific Aim(s): 1) Support multidisciplinary, collaborative projects that pair basic and clinical investigators and draw on expertise of scientists from within and from outside the prostate cancer field. 2) Provide support for pilot projects with high potential to advance prostate cancer research to obtain preliminary data that will form the basis for grant submissions to extramural sponsors.3) Recruit and train early-stage scientists to become the next generation of leaders in translational prostate cancer research through access to mentors that are renowned senior investigators and leaders in basic and clinical arenas, as well as networking opportunities among other project Co-Leaders. 4) Provide world-class infrastructure to carry out innovative, high-quality, high-impact translational prostate cancer research. 5) Support efforts to develop bench-to-bedside discoveries for clinical diagnostics and therapies. 6) Foster collaborations among investigators within the institution and with other institutional SPORES or extramural prostate cancer programs.

Administration Core

Specific Aim(s): 1) Provide scientific, programmatic, and administrative leadership to all aspects of the SPORE. Effective AC leadership is essential to the success of the Michigan Prostate SPORE. The Administration Core is the central decision-making group designed to encourage research productivity, promote interaction and collaboration, and set the vision, direction, and priorities for the Michigan Prostate SPORE. 2) Develop, facilitate, and monitor progress of translational aims with project Co-Leaders. The Clinical Applications Committee, the annual review with the External Advisory Board and Steering Committee, and the monthly meetings between Project Leaders and the PIs function to keep the Michigan Prostate SPORE robust and move the translational objectives forward. All of these interactions are facilitated by the Administration Core. 3) Identify, support, and facilitate scientific collaborations. The Administration Core is charged with creating a culture of collaboration through initiating and implementing successful interactions among those involved in the SPORE program. Formal horizontal and vertical collaborations are encouraged to accomplish research progress and move promising SPORE projects to the next step on the translational/clinical development pathway. 4) Facilitate communication. Effective and timely communication is crucial to the Michigan Prostate SPORE's success. The Administration Core is responsible for facilitating communication between investigators and groups within the Michigan Prostate SPORE as well as among the SPORE network, the NCI, and investigators across the spectrum of translational cancer research. 5) Perform fiscal and data management functions. The Core performs financial management for each SPORE project, core, and development project. The Core also oversees data management, an essential component of clinical research. 6) Provide functional and ethical oversight to projects and cores and coordinate patient advocacy. The Core provides support and oversight to ensure that all investigators have IRB and animal approvals in place to conduct research. The Core also coordinates quality assurance between the tissue banks and clinical databases. The Core will develop and maintain an advocacy portal to the prostate cancer patient community.

Project 1: Targeting Metastatic Prostate Cancer Patients with Biallelic Loss of CDK12
Specific Aim(s): 1) Define the functional relevance of CDK12 loss to prostate cancer biology and identify synthetic lethal targets. 2) Determine the impact of CDK12 ablation on prostate tumor growth and immune response in vivo. 3) Identify molecular determinants of response in the first clinical trials of immune checkpoint blockade for CDK12-mutant mCPRC patients.

Core 2: Biospecimen/Pathology Core
Specific Aim(s): 1) To protect patient welfare. The highest priority is given to assure that no research protocol compromises pathology diagnosis or tumor staging. Patient confidentiality is maintained through use of an IRB-approved database protocol. 2) The acquisition and processing of prostate tissues for research. The Core assures that the widest range of prostate tissues and derived biomolecules (i.e., protein, DNA and RNA) are available from several established and new sources. These include benign prostate tissue from patients without any known prostatic disease (cystoprostatectomy specimens and transplant donor prostates), clinically localized prostate cancer, and metastatic hormone refractory prostate cancer (Michigan Legacy Tissue Program). 3) To provide high quality pathologic review of prostate tissues. Expert GU pathologists assure uniform review of prostate tissue samples. 4) To provide expert pathology consultation for the purpose of designing translational research projects. This service focuses on determining the types of tissues and amount required for the successful completion of the projects. 5) To perform quality assessment of prostate tissues and clinical data. The Core staff regularly evaluates frozen and formalin fixed tissues for adequacy. 6) To develop technology appropriate for pathology-based translational research. In this renewal, FISHbased strategies are being developed to evaluate genomic biomarkers using tissue microarrays; clinical sequencing of genome and transcriptome from patient specimens to identify causative, driving mutations are being introduced and; organoid and patient-derived xenograft models. 7) Provide support to ongoing clinical studies. The Core will continue to provide tissue procurement services and/or high-quality pathology reviews of specimens from patients enrolled in various clinical trials and studies. 8) The maintenance of clinical and pathology data with links to molecular studies. The Core will continue to expand the detailed clinical and pathology database conforming to the National Cancer Institute's Common Data Elements (CDE) guidelines, permitting queries between molecular findings and clinically relevant outcomes.
Contact Information at funding agency: Jennifer S. Meininger, 240-276-6330, jennifer.meininger@nih.gov
Role: Overall Program Director, Core Leader of Administration Core, Basic Co-Leader of Project 1, Core Co-Leader of Core 2 (BioSpecimen Core).

ORSP 19-PAF05802	04/11/19 – 12/31/21	0.01 CM
(MPI: Chinnaiyan and Robinson)	Total Award:	

Multiple Myeloma Research Foundation
Multiple Myeloma Patients - MYDRUG
Goal(s): To carry out the clinical sequencing of 300 patients with advanced multiple myeloma in our CLIA sequencing laboratory.
Specific Aim(s): None
Contact Information at funding agency: Men Yesil, yesilil@themmrd.org, Multiple Myeloma Research Foundation, Inc., 383 Main Avenue, Norwalk, CT 06851.

ORSP 19-PAF05516	04/01/19 – 03/31/24	0.01 CM
(PI: Chinnaiyan)	Total Award:	

The West Side Institute for Science and Education / Prostate Cancer Foundation
VA/PCF Precision Center of Excellence Award - Jesse Brown VA Medical Center
Goal(s): To carry out clinical sequencing of samples from veterans with metastatic prostate cancer in the form of germline, primary tumor, metastatic tissue (acquired under metastasis biopsy protocols) and ctDNA at time of treatment changes in an effort to ascertain DNA alterations which could provide treatment options through industry-sponsored and investigator-initiated studies.

Specific Aim(s): None
Contact Information at funding agency: Kevin Hull, Kevin.Hull@va.gov, Jesse Brown VA Medical Center, 820 S. Damon Ave #151, Chicago, IL 60612.

18VALO03, Research Agreement Dated 10-8-19 10/08/19 – 10/31/23 0.01 CM
(PI: Chinnaiyan) Total Award:
Veterans Education & Research Assoc of MI / Prostate Cancer Foundation
VA/PCF Precision Center of Excellence Award - Ann Arbor
Goal(s): To carry out clinical sequencing of samples from veterans with metastatic prostate cancer in the form of germline, primary tumor, metastatic tissue (acquired under metastasis biopsy protocols) and ctDNA at time of treatment changes in an effort to ascertain DNA alterations which could provide treatment options through industry-sponsored and investigator-initiated studies.
Specific Aim(s): None
Contact Information at funding agency: Birgit Roller, birgit.roller@va.gov, VA Medical Center, Research Service #151, 2215 Fuller Road, Ann Arbor, MI 48105

18VALO10 - ORSP 20-PAF00091 11/18/19 – 11/08/24 0.01 CM
(PI: Chinnaiyan) Total Award:
Bay Pines Foundation, Inc / Prostate Cancer Foundation
VA/PCF Precision Center of Excellence Award - Bay Pines VA Healthcare System
Goal(s): To carry out clinical sequencing of samples from veterans with metastatic prostate cancer in the form of germline, primary tumor, metastatic tissue (acquired under metastasis biopsy protocols) and ctDNA at time of treatment changes in an effort to ascertain DNA alterations which could provide treatment options through industry-sponsored and investigator-initiated studies.
Specific Aim(s): None
Contact Information at funding agency: Eric Abercrombie, Eric. Ambercrombie@va.gov, Executive Director, 10000 Bay Pines Blvd, PO Box 416, Bay Pines, FL 33744

18VALO10 - ORSP 20-PAF03953 2/10/20 – 2/09/25 0.01 CM
(PI: Chinnaiyan) Total Award:
Tampa VA Research and Education Foundation / Prostate Cancer Foundation
VA/PCF Precision Center of Excellence - Tampa VA Research and Education Foundation
Goal(s): To carry out clinical sequencing of samples from veterans with metastatic prostate cancer in the form of germline, primary tumor, metastatic tissue (acquired under metastasis biopsy protocols) and ctDNA at time of treatment changes in an effort to ascertain DNA alterations which could provide treatment options through industry-sponsored and investigator-initiated studies.
Specific Aim(s): None
Contact Information at funding agency: Reeder, Douglas. dreeder@tampavaref.org, 813-780-2623 ext 103

20-PAF07516 (PI: Fearon) 06/01/20 – 5/31/21 0.18 CM
NIH/NCI Total Award:
Enhancement of Data Sharing in Pediatric, Adolescent and Young Adult Cancers
Goals: providing the scientific community access to the genomic data, computational workflows, and clinical processes that enable MI-OncoSeq.
Specific Aim(s): (1) Harmonize and submit our "Pediatric and AYA Cancer Touchstone Dataset", which represents a wealth of real-world integrative genomic and clinical data for over 1,000 qualified patients. (2) Package and distribute the cloud-based computational infrastructure powering bioinformatics analyses of DNA and RNA sequencing data. (3) Document and codify our processes for interpreting n-of-1 genetic and molecular findings in the context of rare and pediatric cancers.
Contact Information at funding agency: Guidry Auvil, Jaime, Jaime.guidryauvil@nih.gov

20-PAF08017 (PI: Fearon) 06/01/20 – 5/31/21 0.18 CM
NIH/NCI Total Award:
Development of National Childhood Cancer Registry
Goals: oversee the contribution of our long-term clinical data as part of the CCDI and plans to enrich our local dataset with additional clinical and genomic information that will be of broad value to the research community.
Specific Aim(s): (1) Identify and aggregate existing comprehensive clinical and genomic data from pediatric and adolescent and young adult (AYA) cancer patients using the Long-Term Pediatric Oncology Database. (2) Perform assessment of data quality and establish processes for correcting missing or inconsistent data. (3) Using well-established informatics tools and approaches, map our cancer data to established standards, and submit the data to the Cancer Research Data Commons or other NCI repositories.
Contact Information at funding agency: Lam, Clara, clara.lam@nih.gov

20-PAF08352 (PI: Chinnaiyan) 12/31/20 – 12/30/22 0.01 CM
Prostate Cancer Foundation Total Award:
Targeting transcriptional addiction in prostate cancer by impeding neo-enhancer accessibility
Goals: To establish a first in man clinical trial of SWI/SNF ATPase degraders in metastatic CRPC patients.
Specific Aim(s): 1) Develop orally bioavailable variants of AU-15330 and optimize its drug-like pharmacokinetic properties. 2) Perform comprehensive toxicology evaluations of AU-15330 and orally bioavailable variants in rats. 3) Determine predictive biomarkers of response to SMARCA2/4 degraders and initiate a Phase I/II trial with AU-15330 in mCRPC patients.
Contact Information at funding agency: Soule, Howard: applications@pcf.org, 310-570-4596
****New Support****

PENDING:
Project Number: N/A Chinnaiyan (PI) 0.01 CM
PKUHSC Joint Institute Total Award: 02/01/20 – 01/31/22 Contact Information at funding agency: Huang, Amy: yanhuang@umich.edu, 734-763-6461
Michigan-Peking Cancer Biomarker Collaborative
Goals: To leverage our previous discoveries to generate a novel expanded quantitative PCR-based MiPS assay (MiPS-QPCR) and a next-generation sequencing-based MiPS assay (MiPS-NGS) that can detect high grade prostate cancer non-invasively with urine samples.

20-PAF08390 (PI: Salami) 09/01/20 – 8/31/22 0.6 CM
Prostate Cancer Foundation Total Award
Seeing the Unseen: Using Machine Learning and Molecular Profiling to Characterize Prostate Cancer Visibility on Multiparametric MRI
Specific Aim(s): to develop a machine learning algorithm for the detection of mpMRI visible and invisible GG ≥2 PCa and to characterize the molecular basis of high grade cancer visibility on mpMRI. In a pilot cohort using a targeted sequencing approach, we observed that the molecular profile of mpMRI visible and invisible cancer foci are indistinguishable, indicating that image-guided biopsy strategies and therapeutic interventions may miss biologically relevant cancer foci.
Contact Information at funding agency: Lam, Clara, clara.lam@nih.gov

21-PAF05225 (PI: Malek) 12/01/21 –11/30/26 0.24 CM
NIH Total Award:
Development of clinical grade ddPCR assays for AML MRD monitoring
Goals: UH2 phase (years 1-2): To develop highly sensitive and specific multiplexed droplet digital PCR assays for the frequently mutated AML driver genes NPM1, IDH1, IDH2, K-RAS and N-RAS. UH3 phase (years 3-5):

To measure mutant NPM1, IDH1, IDH2, K-RAS and N-RAS variant allele frequencies (VAFs) in two large AML patient cohorts using clinical grade ddPCR assays.
Specific Aim(s): 1) To develop highly sensitive and specific droplet digital PCR assays for the frequently mutated AML driver genes NPM1, IDH1, IDH2, K-RAS and N-RAS. 2) To measure mutant NPM1, IDH1, IDH2, K-RAS and N-RAS variant allele frequencies (VAFs) in two large AML patient cohorts using clinical grade ddPCR assays.
Contact Information at funding agency: Shane Woodward, Woodwars@mail.nih.gov 240-267-6303

PREVIOUS:
15CHAS07 (PI: Chinnaiyan) 10/01/15 – 03/12/20 (NCE) 0.0 CM
Prostate Cancer Foundation
Prostate Cancer Foundation Dream Team Continuation of the CRPC 500 Cohort Study
Specific Aim(s): 1) Continue to gather clinical follow-up on patients enrolled on the CRPC 500 cohort. This will fund the clinical coordination site to maintain data collection across the multi-institutional cohort. To help facilitate access of this data by the research community we will establish a "Data Sharing Core" to enable easy access and sharing of the sequence data along with valuable clinical parameters across the consortium. We will explore the use of commercial cloud based infrastructure to support this initiative. 2) Identify 150 patients out of 500 from the CRPC500 study who have progressed for re-biopsy and whole exome and transcriptome sequencing analysis. This will allow us to assess tumor evolution and decipher molecular mechanisms of resistance. Matched progression biopsies will markedly increase the statistical power to attribute causality to alterations identified. 3) Identify and sequence 150 CRPC patients that have progressed post-abiraterone and/or postenzalutamide. This will allow us to establish the molecular landscape of a post-Abi/post-Enza cohort of patients. Compare molecular and morphological alterations with the West Coast Dream Team.
Contact Information at funding agency: Dr. Howard Soule, applications@pcf.org, Prostate Cancer Foundation, 1250 4th Street, Santa Monica, CA 90401

3-P30-CA046592 (PI: Fearon) 06/01/20 – 12/31/20 0.48 CM
NIH/NCI yr
Targeting TMPRSS2 expression as a therapy for coronavirus infection and replication
Specific Aim(s): To provide a pre-clinical rationale to evaluate drugs that suppress lung epithelial TMPRSS2 expression to treat or prevent coronavirus.
Contact Information at funding agency: Ptak, Krzysztof: krzysztofptak@mail.nih.gov
****Support Ended****

Award No: N/A (PIs: Chinnaiyan and Heath) 12/31/16 – 12/31/19 0.12 CM
Prostate Cancer Foundation (NCE) yr
Development of an Autophagy Inducing Multi-Tyrosine Kinase Inhibitor ESK981 in the Treatment of Castration Resistant Prostate Cancer
Specific Aims: 1) To explore the mechanism of action of ESK981 in castration resistant prostate cancer; 2) To investigate the efficacy of ESK981 in pre-clinical models of castration resistant prostate cancer; and 3) To initiate a Pilot Phase II study of ESK981 in metastatic castration resistant prostate cancer. UM will be responsible for Aims 1 and 2 and also biomarker development for pre-clinical study in vivo in Aim 3.
Contact Information at funding agency: Dr. Howard Soule, applications@pcf.org, Prostate Cancer Foundation, 1250 4th Street, Santa Monica, CA 90401

W81XWH-12-1-0080 (PI: Chinnaiyan and Li) 09/15/12 – 09/14/19 (NCE) 0.12 CM
Department of Defense yr
Collaborative Innovators Award: Advancing our understanding of the etiologies and mutational landscapes of basal-like, luminal A, and luminal B breast cancers
Goal(s): Sequencing of samples to find mutations; correlate with clinical pathologic and epidemiologic factors

Specific Aim(s): 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.
Contact Information at funding agency: Cheryl A. Lowery, U.S. Army Medical Research Acquisition Activity, 820 Chandler Street (MCMR-AAA-R), Fort Detrick, MD 21702-5014, 301-619-7150, Cheryl.Lowery@us.army.mil

W81XWH-14-1-0555 (MPI: Chinnaiyan) 09/22/14 – 09/21/18 (NCE) 0.6 CM
Department of Defense yr
Development of Personalized Cancer Therapy for Men with Advanced Prostate Cancer
Specific Aim(s): 1) Develop PDXs that reflect the lethal form of PCa; 2) Develop a responder ID profile hypothesis according to the treatment responsiveness of fully characterized PCa PDXs; 3) Validate the responder ID profile hypothesis in a clinical trial
Goal(s): 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.
Contact Information at funding agency: Peggie Lesnow, 820 Chandler Street, Fort Detrick, MD, 21702, Phone: 301-619-2367, Email: margaret.a.lesnow.civ@mail.mil

U01-HL-126499 (PI: Tewari) 08/01/14 – 08/31/18 0.48 CM
NIH, NHLBI yr
Reference Profiles of ExRNA in Biofluids from Well-Defined Human Cohorts
Specific Aim(s): 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.
Goal(s): To generate quality-controlled, comprehensive RNA sequencing-based profiles of human body fluids including plasma, serum and urine from healthy individuals.
Role: Co-investigator
Contact Information at funding agency: Tracee Foster Email: gilchrit@mail.nih.gov Phone: 301.402.3843

UM1HG006508 (PIs: Chinnaiyan, Pienta and Robert) 07/19/13 – 05/31/18 (NCE) 1.2 CM
National Institutes of Health yr
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 Aim(s): 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.
Contact Information at funding agency: Harvey, Zephaun, harveyz@mail.nih.gov, 301 435-7859

(MPIs: Chinnaiyan, Wang, Malik) 07/31/15 – 07/30/17 0.12 CM
Prostate Cancer Foundation – Movember Challenge Award
Targeting the MLL complex for the development of new therapeutics for CRPC
Specific Aim(s): 1) To design and develop small molecular inhibitors of the menin-MLL interaction with improved potency in prostate cancer models and optimized drug-like properties for clinical development; 2) To study the mechanism of pharmacologic inhibition of the menin-MLL interaction in prostate cancer cells; 3) To establish in vivo efficacy of menin inhibitors in animal models of prostate cancer.
Goal(s): to discover and develop new small-molecule inhibitors for the treatment of advanced lethal prostate cancer by targeting MMSET.
Contact Information at funding agency: Dr. Howard Soule, applications@pcf.org, Prostate Cancer Foundation, 1250 4th Street, Santa Monica, CA 90401

U01CA183027 (PIs: Chinnaiyan, Linehan) 02/11/14 - 01/31/17 1.2 CM
NIH
Integrative molecular imaging and sequencing of prostate cancer
Goal(s)/Aim(s)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.
Contact Information at funding agency: Henderson, Lori A., hendersonlori@mail.nih.gov, 240.276.5930

PC121111 (PI: Scher, H.) 09/30/13 – 09/29/16 0.91 CM
Department of Defense
Toward the Practice of Precision Medicine: Multicenter Validation of Biomarker Assays for Clinical Management of Prostate Cancer
Goal(s): Establish and validate TMPRSS2:ERG assays; Validate the utility of the TMPRSS2:ERG TMA assay for the non-invasive detection of clinically significant prostate cancer in urine; Validate the ERG rearrangement FISH assay on tissues and determine the prevalence of ERG rearrangements in isolated precursor and diagnostically challenging lesions
Specific Aim(s): 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

AACR (Dream team leader: Chinnaiyan) 08/01/12 – 07/31/16 (NCTX) 0.6 CM
Stand up to Cancer & Prostate Cancer Foundation Dream Team
Precision Therapy of Advanced Prostate Cancer
Goal(s): The overall goal of this proposal is to catalyze the interaction of a multi-disciplinary team of investigators, with a track record of accomplishments in prostate cancer research, to work together on the challenging problem of metastatic castration resistant prostate cancer (CRPC).

Specific Aim(s): 1) Establish a multi-institutional infrastructure incorporating 5 leading prostate cancer clinical sites, 2 sequencing and computational analysis sites, linked with appropriate sample and data coordination; 2) Establish a prospective cohort of 500 patients (the "CRPC 500") utilizing the multi-institutional infrastructure to support the clinical use of integrative prostate cancer sequencing, analysis, and clinical trial decision making; 3) Conduct parallel, preclinical *in vivo* functional studies of resistance biomarkers and of SU2C-PCF sponsored combination therapies; 4) Identify molecular determinants of abiraterone sensitivity and acquired resistance in patients; 5) Conduct clinical trials of novel combinations targeting AR and/or the PTEN pathway, based on existing preclinical data and an understanding of resistance mechanisms; 6) Identify molecular determinants of sensitivity and acquired resistance to PARP inhibitors in patients.
Contact Information at funding agency: Frederic Biemar, frederic.biemar@aacr.org, (215) 446-7261

R01 CA154365 (PIs: Beer and Chinnaiyan) 04/01/11 – 03/31/16 0.36 CM
National Institutes of Health
Identification and Characterization of Gene Fusions in Lung Adenocarcinoma
Goal(s): This proposal will identify new gene-fusions in lung cancer utilizing a newly developed bioinformatics approach combined with next-generation sequencing data.
Specific Aim(s): 1) Functional characterization of the R3HDM2-NFE2 gene fusion in H1792 lung cancer cells, 2) Determine the frequency of occurrence in primary lung cancer and functionally characterize the novel HSPA1ANFKBIL1; 3) Functional characterization of novel gene fusions in lung cancer.
Contact Information at funding agency: Rebecca Brightful, **Email**: brightfr@mail.nih.gov **Phone**: 301-631-3011 **Fax**: 301-451-5391

R01 CA125612 (PI: Rubin) 04/01/13 - 03/31/16 0.24 CM
NIH
Towards Understanding Prostate Cancer Heterogeneity
Goal(s): Determine protein-protein interactions and subsequent signaling cascades with mass spectrometry
Specific Aim(s): 1) To determine the substrate specificity of prostate cancer-derived SPOP mutants; 2) To determine the downstream pathways deregulated by SPOP mutations; 3) To establish the prevalence of SPOP mutation, its relation to other molecular changes, and its significance to patient outcomes in multiple populations of prostate cancer.
Contact Information at funding agency: Michelle Lewis, Joan & Sanford I Weill Medical College of Cornell University, 1300 York Avenue, New York, NY 10085
Role: Co-Investigator

OTHER SUPPORT

TOMLINS, SCOTT

CURRENT

P50CA186786 (PI: Chinnaiyan) 09/11/14 - 08/31/24 0.6 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.
Role: Co-Leader of Project 2

1UO1CA21417 (PI: Chinnaiyan) 09/01/2016 – 08/31/2021 NIH 0.6 cal mos

Discovery and qualification of transcriptomic biomarkers for the early detection of aggressive prostate cancer
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.
Role: Co-Investigator

PREVIOUS

PC141474 (PI: Tomlins and Schaeffer) 09/30/15 – 09/29/18 .96 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

U01 CA179106 (Hadjiyski) 05/15/14 - 04/30/18 0.6 cal mos
NIH salary support only
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.
Role: Co-Investigator

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.

R01 CA181605 (PI: Nelson) 01/01/14 - 12/31/18 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.
Role: Co-Investigator

R01 DK106618 (PI: Rainey/Tomlins) 03/01/16 - 02/28/21 1.10 cal mos
NIH
Adrenal Origins of Aldosterone Excess
Goal(s): Test the hypothesis that APAs arise from a population of dysplastic adrenal cells (APCC) present in the majority of adults that harbor somatic mutations leading to autonomous aldosterone production. The proposed study will provide a detailed understanding of the molecular steps that cause primary aldosteronism (PA).

1 R01 CA196619 (PI:Cho) 05/01/16 – 04/30/19 .30 cal mos
NIH/NCI
Credentialing murine ovarian cancer models for translational applications
This application was submitted in response to a funding opportunity intended to support projects that enhance applicability of mouse models for translational research. The proposed research will use a cross-species (mouse-human) validation strategy to credential novel ovarian cancer models and employ the Oncology Models Forum to improve and promote the use of mouse models of ovarian cancer for translational applications.
Role: Co-I

1UO1CA21417 (PI: Chinnaiyan/Tomlins) 09/01/2016 – 08/31/2021 1.2 cal mos
NIH
Discovery and qualification of transcriptomic biomarkers for the early detection of aggressive prostate cancer
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.
Role: PI

NIH (PI: Rubin) 04/01/2017 – 03/31/2022 0.6 cal mos

Towards Understanding the Genomic Heterogeneity of Metastatic Prostate Cancer (SPORE Project)
Goal(s): As part of the Weill Cornell Medical College S.P.O.R.E., this project aims to assess a large cohort of paired primary ADT-naïve and metastatic CRPC specimens to understand and exploit the molecular

mediators of PCa progression to inform on optimal clinical pathologic practice, identify biomarkers, and inform on disease biology.
Role: Project Co-Leader (Co-Investigator)