

AWARD NUMBER: W81XWH-19-1-0407

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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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 will 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 will 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 (task 100% complete).

Obtain HRPO approval (months 3-4)

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

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

Hematoxylin and eosin (H&E) slides for study specimens were retrieved from the pathology archive, and Dr. Udager has begun to review these specimens to select tissue for analysis (task approximately 25% complete).

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

Nothing to report.

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

Nothing to report.

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)

Nothing to report.

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

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 radical prostatectomy tissue for analysis. Then we will perform ERG/PTEN and ERG/SPINK1 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.

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

HRPO study approval took longer than expected, and by the time we were able to start working on the project, we had to shut down all in-person research activities due to the COVID-19 pandemic. My laboratory and other research facilities at our institution were completely shut down for 3 months and were only gradually re-opened over the final 2-3 months of the reporting period. During the research shutdown, we were able to identify study specimens from clinical databases, and once research facilities re-opened in June 2020, we were able to begin to retrieve and review study specimens.

Changes that had a significant impact on expenditures

Due to longer than expected HRPO study approval and then the laboratory shutdown due to the COVID-19 pandemic, we have delayed hiring a research technician to work on the study; however, we plan to hire someone for this position in the next reporting period.

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 has led all aspects of the study, including: obtaining approval from the Department of Defense HRPO; and, identifying, obtaining, and review study cases.
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 assisted in obtaining HRPO approval and oversaw database queries to identify study cases.
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

Joint Institute for Translational and Clinical Research Amy Huang	Salami/Palapattu/Morgan/Gong (PI) \$590,579 total award amount	0.60 CM 9/2017-6/2021
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Comprehensive Molecular Profiling of Renal Cell Carcinoma

Goal(s): The goal of this project is to characterize the genomic landscape of clear cell renal cell carcinoma and identify predictive biomarkers of recurrence.

Role: Co-Investigator

P50 CA186786 NIH/NCI Jennifer Meininger Grants Management Specialist	Chinnaiyan (PI) \$140,000 total award amount	1.20 CM 11/2018-10/2020
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Integrative targeted next-generation DNA and RNA sequencing of multiclonal prostate cancer index nodules: implications for molecular biomarker assessment

Goal(s): The goal of this project is to utilize integrative targeted next-generation DNA and RNA sequencing to examine the effect of index tumor nodule multiclonality on detection of common clinically-relevant molecular alterations and determine its impact on calculation of established gene expression-based prognostic assays.

Role: Recipient of Michigan Prostate SPORE Career Enhancement Program Sub-Award

R37 CA222829 NIH/NCI Jennifer Meininger Grants Management Specialist	Xu (PI) \$332,648	0.12 CM 1/2019-12/2023
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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.

Role: Co-Investigator

U01 CA232931 NIH/NCI Jennifer Meininger Grants Management Specialist	Hadjiyski/Alva (PI) \$425,764	0.24 CM 5/2019-4/2024
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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.

Role: Co-Investigator

W81XWH-19-1-0407
Department of Defense
Tom Winter
Grants Management Specialist

Udager (PI)
\$1,169,017 total award amount

3.66 CM
9/2019-8/2023

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.

P50 CA186786
NIH/NCI
Jennifer Meininger
Grants Management Specialist

Chinnaiyan (PI)
\$1,191,863

0.60 CM
9/2019-8/2024

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.

Role: Co-Investigator (Project 2 and Project 4)

****New Support****

W81XWH-20-1-0405
Department of Defense
Grants.Gov Customer Support

Alumkal (PI)
\$1,170,000 total award amount

0.60 CM
9/2020-8/2023

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.

Role: Co-Investigator

****New Support****

R01 CA251245
NIH/NCI
Crystal Wolfrey
Grants Management Specialist

Alumkal (PI)
\$394,446

0.60 CM
9/2020-8/2025

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.

Role: Co-Investigator

****New Support****

PREVIOUS

W81XWH-14-1-0466
Department of Defense
Theresa Miller, PhD
Grants Management Specialist

Tomlins (PI)
1/2017-9/2017

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.

Role: Co-Investigator

University of Michigan

Rogel Cancer Center

Shauna Goble

smgoble@umich.edu

734-936-9603

Udager (PI)

9/2017-12/2019

Integration of Multimodal Pre-Operative Biomarkers for Optimizing the Clinical Management of Aggressive Bladder Cancer

Goal(s): The goal of this project is to assess the impact of integration of multimodal pre-operative biomarkers on predicting complete response to neoadjuvant chemotherapy in patients with aggressive bladder cancer.

****Support Ended****

OTHER SUPPORT

MEHRA, ROHIT

CURRENT:

1U01CA214170-01 (PI: Chinnaiyan) 09/15/16 – 08/31/21 0.48 Calendar MO
NIH/NCI \$372,000/yr Source Country: USA

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.

Role: Co-Investigator

Program Official: Jacob Kagan

2 P50 CA186786-06 09/03/2019 – 08/31/2024 0.30 Calendar MO
NCI/NIH (PI: Chinnaiyan) Source Country: USA

Annual Direct: \$1,191,863 Total Award: \$9,215,218

Michigan Prostate SPORC: Biospecimen/Pathology Core

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.

Role: Co-I

Program Official: Julia Arnold

****New Support****

W81XWH1910424 09/01/2019 – 08/31/2022 0.30 Calendar MO
DOD (PI: Pitchiaya) Source Country: USA

Annual Direct: \$184,452 Total Award: \$936,000

Unraveling tumor microenvironment heterogeneity in advanced prostate cancer

Major Goals: 1) Investigate the evolution of tumor microenvironment during PCa progression. Temporally profile genetically engineered mouse (GEM) models of aggressive PCa (Pten^{-/-}, and High-Myc), to characterize the evolution and diversity of cancer cells, immune infiltrates and cancer-associated fibroblasts. 2) Understand the impact of therapeutic intervention on tumor microenvironment. Investigate the impact of immunotherapeutic drugs on cell type composition of tumors in GEM and syngeneic mouse (MycCaP) xenograft models. 3) Create a human prostate tumor cell atlas to stratify aggressive PCa subtypes in the general and veteran population. Use SCA to profile normal human prostates, localized PCa and metastatic castration resistant PCa (mCRPC) to identify the spatial co-ordinates of distinct tumor cell types.

Role: Co-I

Grants Specialist: Thomas Winter

****New Support****

W81XWH-19-10407 09/01/2019 – 08/31/2023 0.60 Calendar MO
DOD (PI: Udager) Source Country: USA

Annual Direct: \$148,882 Total Award: \$1,169,017

Intratumoral heterogeneity of aggressive molecular biomarkers in lethal primary prostate cancer

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.

Role: Co-I

Grants Specialist: Thomas Winter

1 R01 CA240991-01

09/01/2019 – 08/31/2024

0.36 Calendar MO

NCI/NIH (PI: Morgan)

Source Country: USA

Annual Direct: \$402,521

Total Award: \$3,018,336

Determining the clinical impact of gene expression testing in localized prostate cancer

To do this, we propose the following aims:

Specific Aim 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.

Specific Aim 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.

Specific Aim 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.

Role: Co-I

Program Official: Erica Breslau

****New Support****

5 P01 CA093900-15

7/2/2020 – 5/31/2025

1.00 Calendar MO

NCI/NIH (PI: Keller)

Source Country: USA

Annual Direct: \$1,072,376

Total Award: \$7,440,901

The Biology of Prostate Cancer Skeletal Metastases: Core C (Bone Core)

Major Goals: 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 will provide valuable information and consistency across the projects in the program.

Role: Pathologist

Program Official: Joanna Watson

****New Support****

PAST:

W81XWH-16-1-0314

7/01/2016 – 6/30/2019

DOD (PI: Mehra)

Discovery and characterization of PRCAT47: A novel prostate lineage and cancer specific long non-coding RNA (PC150246)

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).

P01 CA093900

6/17/2015 – 5/31/2020

NIH (PI: Keller)

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

Role: Pathologist of Core 3 (Bone Core)

****Support Ended****

W81XH1520018

6/15/2015 – 6/14/2018

Department of Defense (PI: Hussain)

PCCTC Affiliate Clinical Research Sites - The University of Michigan Site

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.

Role: Co-Investigator

OTHER SUPPORT

SIDDIQUI, JAVED

CURRENT

U01 CA214170 09/15/16 – 08/31/21 2.4 CM
NIH/NCI (PI: Chinnaiyan) \$372,001/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
Role: Technical Director

W81XWH-19-1-0407 09/01/19 - 08/31/23 1.2 CM
DOD (PI: Udager) \$749,370/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
Role: Co-Investigator

P50 CA186786 09/11/14 - 08/31/24 0.6 CM
NIH/NCI (PI: Chinnaiyan, Palapattu, Heath) \$1,467,846/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 Role: Technical Director of Tissue Core
****New Support****

R35 CA231996 9/1/18 – 8/31/25
NIH/NCI (PI: Chinnaiyan) \$928,651/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 EDNR'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

Role: Technical Director

PREVIOUS:

NIH

04/01/18-03/31/20

\$1,210,008

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

****Support Ended****

15CHAS07 (PI: Chinnaiyan)

10/01/15 – 03/12/20

Prostate Cancer Foundation

\$500,000/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 Prostate Cancer Foundation, 1250 4th Street, Santa Monica, CA 90401

Role: Technical Director

****Support Ended****

PREVIOUS/CURRENT/PENDING

CHINNAIYAN, A.M.

CURRENT

R35CA231996 (PI: Chinnaiyan) 09/01/18 – 08/31/25 6.0 CM
National Institutes of Health \$582,000/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: None.

Contact Information at funding agency: Tawnya McKee

U24CA210967 (MPIs: Chinnaiyan, Nesvishkii, Dhanasekaran) 09/15/16 – 08/31/21 0.6 CM
NIH \$487,901/yr

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

1U01CA214170-01 (MPI: Chinnaiyan) 09/15/16 – 08/31/21 1.8 CM
NIH/NCI \$360,840/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

1 R01 CA200660-01A1 (PIs: Grembecka, Chinnaiyan) 08/01/16 - 07/31/21 0.48 CM
NIH/NCI \$233,568/yr

Targeting the MLL complex in Castration Resistant Prostate Cancer

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.

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

Contact Information at funding agency: Elesinmogun, Funmi

P50 186786 (PI: Chinnaiyan, Palapattu, Heath)) 09/11/14 - 08/31/24
NIH/NCI \$1,191,863/yr

2.4 CM

Michigan Prostate SPORE

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) To assess the utility of MiPS-NGS as a prostate cancer early detection assay in men at high genetic risk. 2) To determine whether MiPS-NGS can predict grade progression in men on active surveillance.

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, **Role:** Overall Program Director, Core Leader of Administration Core, Basic Co-Leader of Project 1, Core Co-Leader of Core 2 (BioSpecimen Core).

****New Support****

15CHAS07 (PI: Chinnaiyan)	10/01/15 – 03/12/20 (NCE)	0.0 CM
Prostate Cancer Foundation	\$500,000/yr	

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, Prostate Cancer Foundation, 1250 4th Street, Santa Monica, CA 90401

ORSP 19-PAF05802	04/11/19 – 12/31/20	0.0 CM
(MPI: Chinnaiyan and Robinson)	\$595,500/yr	

Multiple Myeloma Research Foundation

Multiple Myeloma Patients - MYDRUG

Specific Aim(s): To carry out the clinical sequencing of 300 patients with advanced multiple myeloma in our CLIA sequencing laboratory.

Contact Information at funding agency: Men Yesil, Multiple Myeloma Research Foundation, Inc., 383 Main Avenue, Norwalk, CT 06851.

ORSP 19-PAF05516	04/01/19 – 03/31/24	0.0 CM
(PI: Chinnaiyan)	\$226,800/yr	
The West Side Institute for Science and Education / Prostate Cancer Foundation		
<i>VA/PCF Precision Center of Excellence Award - Jesse Brown VA Medical Center</i>		
<u>Specific Aim(s):</u> 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.		
<u>Contact Information at funding agency:</u> Kevin Hull Jesse Brown VA Medical Center, 820 S. Damon Ave #151, Chicago, IL 60612.		

18VALO03, Research Agreement Dated 10-8-19	04/01/19 – 03/31/24	0.0 CM
(PI: Chinnaiyan)	\$226,800/yr	
Veterans Education & Research Assoc of MI / Prostate Cancer Foundation		
<i>VA/PCF Precision Center of Excellence Award - Ann Arbor</i>		
<u>Specific Aim(s):</u> 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.		
<u>Contact Information at funding agency:</u> Birgit Roller, VA Medical Center, Research Service #151, 2215 Fuller Road, Ann Arbor, MI 48105		

18VALO10 - ORSP 20-PAF00091	11/18/19 – 11/08/24	0.0 CM
(PI: Chinnaiyan)	\$226,800/yr	
Bay Pines Foundation, Inc / Prostate Cancer Foundation		
<i>VA/PCF Precision Center of Excellence Award - Bay Pines VA Healthcare System</i>		
<u>Specific Aim(s):</u> 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.		
<u>Contact Information at funding agency:</u> Eric Abercrombie, Executive Director 10000 Bay Pines Blvd, PO Box 416, Bay Pines, FL 33744		
New Support		

18VALO10 - ORSP 20-PAF03953	2/10/20 – 2/09/25	0.0 CM
(PI: Chinnaiyan)	\$226,800/yr	
Tampa VA Research and Education Foundation / Prostate Cancer Foundation		
<i>VA/PCF Precision Center of Excellence - Tampa VA Research and Education Foundation</i>		
<u>Specific Aim(s):</u> 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.		
<u>Contact Information at funding agency:</u> Reeder, Douglas		
New Support		

PREVIOUS:

Award No: N/A (PIs: Chinnaiyan and Heath)	12/31/16 – 12/31/19 (NCE)	0.12 CM
Prostate Cancer Foundation	\$500,000/yr	
<i>Development of an Autophagy Inducing Multi-Tyrosine Kinase Inhibitor ESK981 in the Treatment of Castration Resistant Prostate Cancer</i>		

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 Prostate Cancer Foundation, 1250 4th Street, Santa Monica, CA 90401

****Support Ended****

W81XWH-12-1-0080 (PI: Chinnaiyan and Li) 09/15/12 – 09/14/19 (NCE) 0.12 CM
Department of Defense \$589,661/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

****Support Ended****

W81XWH-14-1-0555 (MPI: Chinnaiyan) 09/22/14 – 09/21/18 (NCE) 0.6 CM
Department of Defense \$125,978/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

U01-HL-126499 (PI: Tewari) 08/01/14 – 08/31/18 0.48 CM
NIH, NHLBI \$112,197/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

UM1HG006508 (PIs: Chinnaiyan, Pienta and Robert) 07/19/13 – 05/31/18 (NCE) 1.2 CM
National Institutes of Health \$813,023/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

(MPIs: Chinnaiyan, Wang, Malik) 07/31/15 – 07/30/17 0.12 CM
Prostate Cancer Foundation – Movember Challenge Award \$194,495/yr

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, Prostate Cancer Foundation, 1250 4th Street, Santa Monica, CA 90401

U01CA183027 (PIs: Chinnaiyan, Linehan) 02/11/14 - 01/31/17 1.2 CM
NIH \$257,334/yr

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 \$300,000/yr

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 \$538,355/yr

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 \$92,500/yr

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

R01 CA125612 (PI: Rubin) 04/01/13 - 03/31/16 0.24 CM
NIH \$27,400/yr

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

No Award # (PIs: Chinnaiyan, Wang, Stuckey) 10/01/12 – 10/15/15 (NCTX) 0.12 CM
Prostate Cancer Foundation \$252,002/yr

PCF Honorable A. David Mazzone Challenge Award: *Targeting ERG Fusion Protein for New Prostate Cancer Therapy*

Specific Aim(s): 1) Design of more potent and cell-permeable peptidomimetics targeting ERG; 2) Discovery and optimization of non-peptide small molecule inhibitors targeting ERG; 3) Characterization of candidate small molecules targeting ERG

Goal(s): discover and develop a new therapy for the treatment of prostate cancer by targeting ERG fusion protein in prostate cancer

Contact Information at funding agency: Dr. Howard Soule, Prostate Cancer Foundation, 1250 4th Street, Santa Monica, CA 90401

U01CA111275 (PIs: Chinnaiyan and Rubin) 08/01/10 – 06/30/15 1.2 CM
NIH/NCI \$486,120/yr

Early Detection Research Network: A Systems Biology Approach to the Development of Cancer Biomarkers

Goal(s): Develop “Omics based approaches to study solid tumor for the purpose of developing biomarkers.

Specific Aim(s): Platform technologies cover epigenetics, genomics, transcriptomics, proteomics and metabolomics.

Contact Information at funding agency: Jennifer Edwards, Jennifer.Edwards1@nih.hhs.gov

W81XWH-08-0110 (PI: Chinnaiyan) 09/01/08 – 08/31/13 2.28 CM
Department of Defense – Era of Hope \$500,000/yr

A Search for Gene Fusions/Translocations in Breast Cancer

Specific Aims: 1) develop high-throughput adaptations of existing methodologies such as fluorescence in situ hybridization (FISH), 2) employ bioinformatics and associated analytical tools to elucidate recurrent gene fusions in breast cancers, 3) employ next generation whole transcriptome sequencing of breast tumors.

Contact Information at funding agency: Grants Officer: Cheryl A. Lowery U.S. Army Medical Research Acquisition Activity, 820 Chandler Street (MCMR-AAA-R), Fort Detrick, MD 21702-5014 0284

W81XWH-11-1-0337 (PI: Chinnaiyan) 09/30/11 – 09/29/15 1.2 CM
Department of Defense \$145,145/yr

Prostate Cancer Research Program Idea Development Award, Established Investigator

Discovery of Novel Gene Elements Associated with Prostate Cancer Progression

Goal(s): determine if prostate cancer harbors numerous uncharacterized ncRNAs and show that a subset of these is differentially-expressed transcripts

Specific Aims: 1) to employ next generation sequencing to comprehensively annotate expressed regions in the prostate cancer transcriptome; 2) to validate and characterize transcriptional units in poorly annotated regions; 3) to elucidate a functional and clinical role of poorly-annotated transcripts in prostate cancer.

Contact Information at funding agency: Janet Kuhns U.S. Army Medical Research Acquisition Activity, 820 Chandler Street (MCMR-AAA-R), Fort Detrick, MD 21702-5014

PI: Chinnaiyan 01/01/09 – 12/31/13 0.12 CM
Doris Duke Foundation \$275,000/yr

Distinguished Clinical Scientist Award for Excellence in "Bench to Bedside" Research

Goal(s): to launch a new effort in the laboratory to comprehensively and systematically scour common human solid tumors for the presence of recurrent gene rearrangements. This effort primarily funds the training of new translational researchers under the mentorship of Dr. Chinnaiyan.

Specific Aims: 1) Develop and employ high-throughput fluorescence in situ hybridization (FISH) in order to interrogate solid tumors for recurrent chromosomal aberrations including gene fusions and translocations; 2) Employ bioinformatics and associated analytical tools to elucidate recurrent gene fusions in common solid tumors; 3) Employ next generation whole transcriptome and paired-end sequencing of common solid tumors to identify recurrent gene fusions and integrated non-human sequences that may represent pathogens.

Contact Information at funding agency: Grants Officer: Betsy Myers, Doris Duke Charitable Foundation, 650 5th Avenue, Fl 19, NY, NY

R01CA132874-01 (PI: Chinnaiyan) 03/01/09 – 12/31/13 0.96 CM
NIH/NCI \$166,000/yr

Molecular Sub-typing of Prostate Cancer Based on Recurrent Gene Fusions

Goal(s): Identification of novel molecular subtypes of cancer, characterization of these subtypes, and correlation of these with disease outcome using prostate needle biopsy samples.

Specific Aims: 1) discovery and nomination of novel molecular sub-types of prostate cancer, 2) characterize associations of molecular sub-types of prostate cancer with clinical outcome and/or aggressiveness of disease in a radical prostatectomy cohort, 3) characterize associations of molecular sub-types of prostate cancer with clinical outcome and/or aggressiveness of disease using prostate needle biopsy samples.

Contact Information at funding agency: Grants Management Specialist: Rebecca Brightful, Email:

P50 CA69568 (PI: Chinnaiyan)

06/01/08 - 05/31/13

2.4 CM

NIH/NCI

\$177,509/yr

SPORE in Prostate Cancer

Project 1 Title: *Role of gene fusions in prostate cancer*

Goal(s): determine the role of ETS family gene fusions in prostate cancer cell lines; characterize the phenotype of androgen-regulated ETS transgenic mice.

Specific Aims: 1) Characterization of Oncogenic ETS Gene Fusions in Prostate Cancer; 2) Determine the role of ETS family gene fusions in prostate cancer cell lines; 3) characterize the phenotype of androgen-regulated ETS transgenic mice.

Role: Co-Investigator

Contact Information at funding agency: Andrew Hruszkewycz

OTHER SUPPORT

TOMLINS, SCOTT

CURRENT

P50CA186786 (PI: Chinnaiyan)
NIH

09/11/14 - 08/31/24
\$193,476/yr

0.6 cal mos

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

1U01CA21417 (PI: Chinnaiyan)
NIH

09/01/2016 – 08/31/2021
\$370,065/yr

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)
Department of Defense

09/30/15 – 09/29/18
\$197,443/yr

.96 cal mos

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)
NIH

05/15/14 - 04/30/18
salary support only

0.6 cal mos

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)
NIH

04/03/14 - 02/28/19
\$207,500/yr

2.28 cal mos

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 \$67,200/yr

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 \$349,686/yr

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 \$366,696/yr

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

1U01CA21417 (PI: Chinnaiyan/Tomlins) 09/01/2016 – 08/31/2021 1.2 cal mos
NIH \$370,065/yr

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
\$97,336/yr

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)