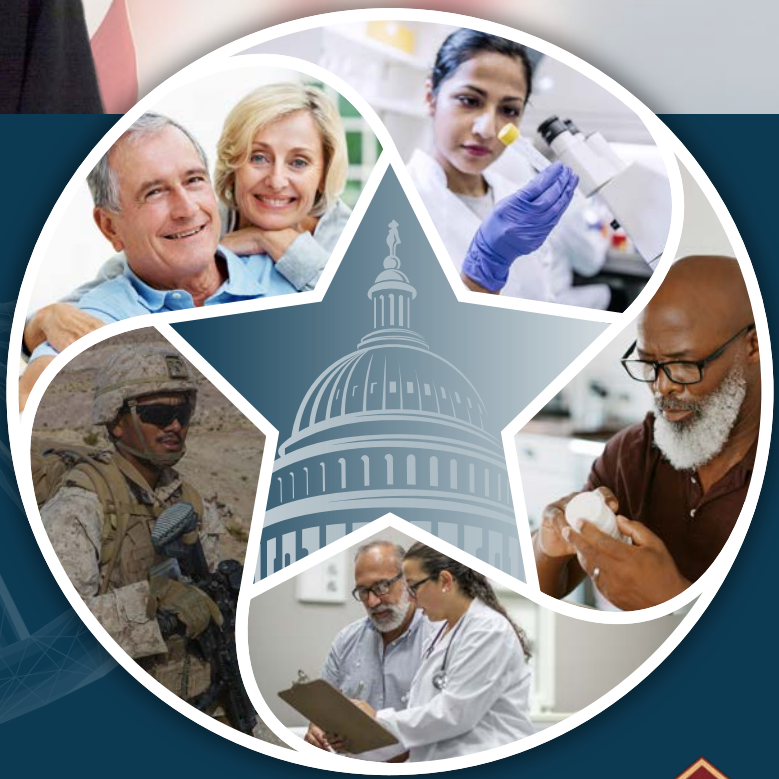
Prostate Cancer Research Program

Congressionally Directed Medical Research Programs

CDMRP

Department of Defense



U.S. Army Medical Research and Development Command

PROSTATE CANCER RESEARCH PROGRAM

The Prostate Cancer Research Program (PCRP) funds research that will lead to elimination of death from prostate cancer and enhance the well-being of Service Members, Veterans, and all men and their families who are experiencing its impact in order to conquer the disease.

Since 1997, Congress has appropriated **$2.04B** to the PCRP for **prostate cancer research**

3,664 research awards

OVERARCHING CHALLENGES

page 6

The PCRP prioritizes research that addresses specific gaps in prostate cancer research and clinical care, with an emphasis on investing in research that will benefit patients diagnosed with lethal prostate cancer or improve quality of life and health equity among men diagnosed with this disease.

INVESTMENT STRATEGY

page 7

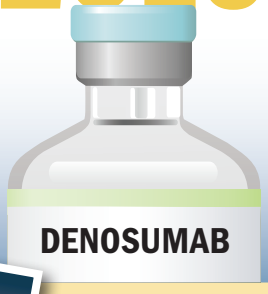
The PCRP has traditionally offered a variety of funding mechanisms that help drive research forward from different approaches, all of which work together to advance the mission of the PCRP.

THE PROSTATE CANCER CLINICAL TRIALS CONSORTIUM (PCCTC)

page 8

The PCCTC is a PCRP-funded network of prostate cancer leaders from top academic medical centers that is utilizing a team-based approach to develop and expedite early-phase clinical testing to bring novel prostate cancer treatments to patients at record speeds. The PCCTC was instrumental in the advancement of three of the four PCRP-supported therapies that are currently impacting patients in the general population and the Military Health System (MHS).

FDA APPROVAL **2010**



DENOSUMAB

FDA APPROVAL **2011**

ABIRATERONE

FDA APPROVAL **2012**

ENZALUTAMIDE

FDA APPROVAL **2018**

APALUTAMIDE

IMPACT OF THE PCRP ON THE MILITARY HEALTH SYSTEM

page 9

80% of active duty population are men

211,625 **Active Service Members** and Department of Defense (DOD) beneficiaries treated for PCa in MHS between 2010–2019

YOUNG INVESTIGATOR AWARD SPOTLIGHTS

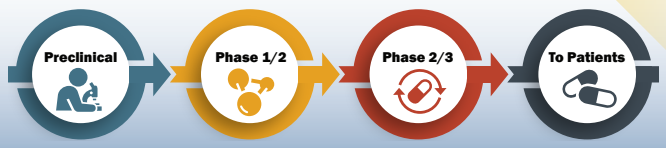
page 10

The PCRP has prioritized investing in the innovative ideas proposed by young investigators. This investment has enabled these investigators to make significant contributions to prostate cancer research and patient care. Many are now helping to mentor the next generation of PCRP-funded new investigators who will further advance prostate cancer research efforts.

IN THE CLINICAL PIPELINE

page 25

The PCRP has invested in the discovery and development of multiple therapies and diagnostic tools since the beginning of the program, many of which have continued to advance through the clinical pipeline spanning from benchtop to bedside.



RESEARCH HIGHLIGHTS

page 13

IMPROVE QUALITY OF LIFE

Preserving Sexual Function in Men Undergoing Radiation Treatment for Prostate Cancer
Tian Liu, Ph.D. and Ashesh Jani, M.D.

DEFINE BIOLOGY OF LETHAL DISEASE

Artificial Lymph Node: A Trap To Study and Fight Prostate Cancer
Liping Tang, Ph.D.

Using A Novel Genetically Engineered Mouse Model to Identify New Drug Targets for Treatment-Resistant Metastatic Prostate Cancer
Lloyd Trotman, Ph.D.

Synergistic Action of Foxp3 and Tsc1 Pathways in Prostate Cancer Progression
Lizhong Wang, Ph.D.

IMPROVING HEALTH EQUITY AND REDUCING DISPARITIES

Investigating Racial Differences in the Financial Impact of Prostate Cancer
James Mohler, M.D.

Investigating the Molecular Differences Leading to Racial Health Disparities in Prostate Cancer Patients
Nallasivam Palanisamy, Ph.D.

Real-Time Visualization of Microscopic Residual Prostate Cancer at the Time of Radical Prostatectomy
Mekhail Anwar, M.D. Ph.D.

DEVELOPING TREATMENTS FOR LETHAL DISEASE

First-in-Class Anti-sMIC Immunotherapy Antibody Therapy to Target Prostate Cancer Metastasis
Jennifer Wu, Ph.D.

BET Bromodomain Degraders for the Treatment of Metastatic Prostate Cancer
Steven Kregel, Ph.D.

Bipolar Androgen Therapy: Breaking Out of the Chrysalis of Chronic Androgen Deprivation Therapy in Men with Late-Stage Castrate-Resistant Prostate Cancer
Samuel Denmeade, Ph.D.

Revolutionizing Prostate Cancer Imaging with Collagen Hybridizing Peptide
Michael Yu, Ph.D.

CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

The office of the Congressionally Directed Medical Research Programs (CDMRP) was born in 1992 from a powerful grassroots effort that resulted in a congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military. Since then, the CDMRP has grown to encompass multiple targeted programs and has received more than $17.8 billion (B) in appropriations from its inception through fiscal year 2021 (FY21). Funds for the CDMRP are added to the DOD budget, in which support for individual programs such as the PCRP is allocated via specific guidance from Congress.

APPLICATION REVIEW PROCESS

The CDMRP uses a two-tier review process for proposal evaluation; both tiers involve dynamic interaction between scientists and disease survivors. The first tier of evaluation is a scientific peer review of proposals to measure them against established criteria for determining their scientific merit. Throughout the history of the PCRP, 400 consumers and 1,842 scientific reviewers have participated in peer review. The second tier is a programmatic review conducted by a Programmatic Panel composed of leading scientists, clinicians, and consumer advocates that compares proposals to each other and makes recommendations for funding based on scientific merit, portfolio balance, and relevance to overall program goals.

David Quinn, M.B.B.S., Ph.D., F.R.A.C.P., F.A.C.P.

FY20 Programmatic Panel Chair, University of Southern California

"For more than 20 years, the program has leveraged cutting-edge prostate cancer biology and innovative clinical trials to reduce the lethality of prostate cancer. Success measured through innovative new drug therapies and better understanding of the underlying mechanisms of prostate cancer risk and response is uniquely focused and delivered to prostate patients and their families through the PCRP."

PROSTATE CANCER RESEARCH PROGRAM

SUMMARY OF OUR HISTORY

In 1997, $45 million (M) was appropriated to the DOD to conduct research in prostate cancer. The funds were to be administered by the DOD PCRP to support meritorious scientific investigations toward the goal of eliminating prostate cancer. This new venture in prostate cancer research was born out of grassroots efforts by dedicated and energized prostate cancer advocates and supporters who worked to realize additional research funds for prostate cancer. To date, this undertaking has resulted in a total appropriation of over $2.04B for the PCRP, including $110M in FY21. This unique partnership among Congress, the military, and prostate cancer survivors, clinicians, and scientists has changed the landscape of biomedical study and energized the research community to conduct high-risk investigations that are more collaborative, innovative, and impactful on prostate cancer.

VISION

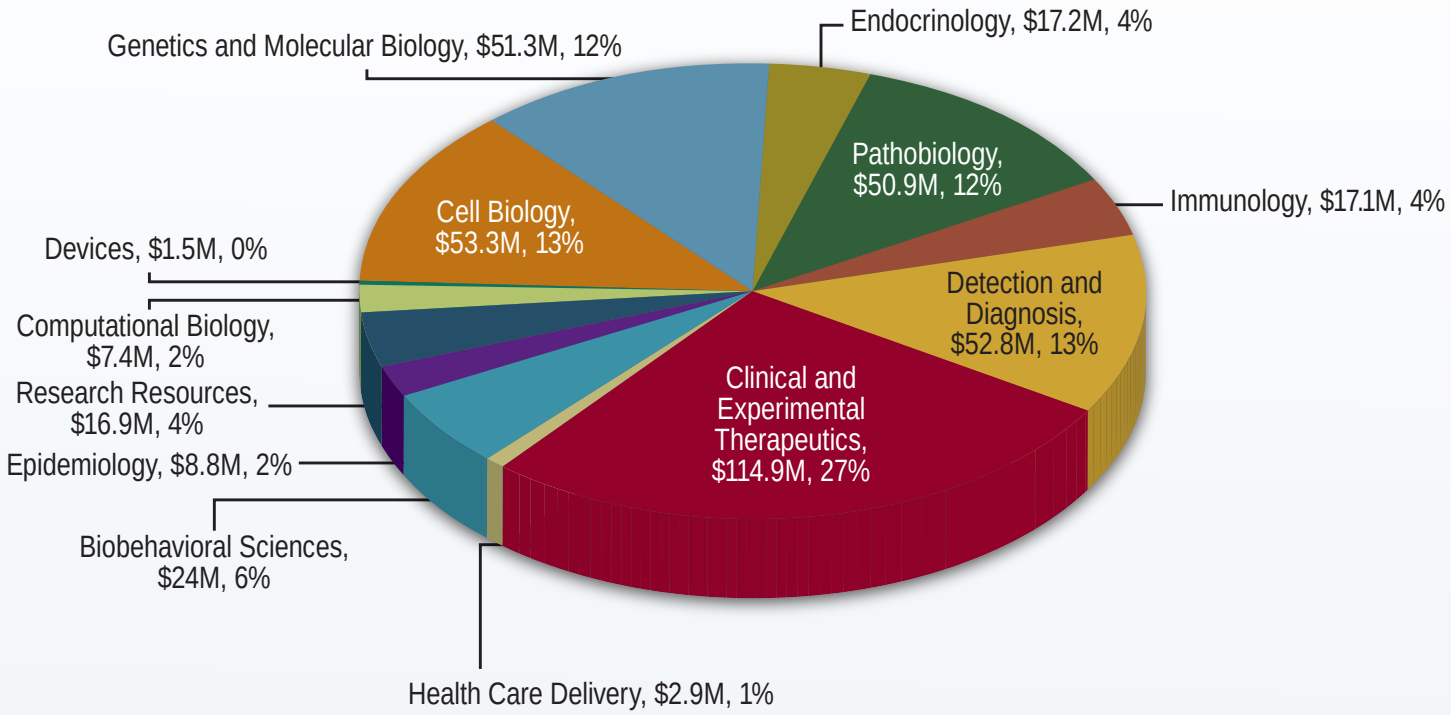
Conquer prostate cancer

MISSION

Fund research that will lead to the elimination of death from prostate cancer and enhance the well-being of Service Members, Veterans, and all the men and their families who are experiencing the impact of the disease

From 1997–2020, the PCRP funded 3,664 research awards. The PCRP strives to diversify its research portfolio to address the critical needs of prostate cancer patients from different scientific approaches. By targeting underrepresented avenues of research and novel applications of existing techniques, the PCRP is able to achieve innovative solutions to critical challenges faced by patients with prostate cancer, ultimately helping to realize the goal of making a direct, positive impact on patients and their families.

FY16–FY20 PCRP RESEARCH PORTFOLIO



ON A MISSION TO CONQUER PROSTATE CANCER

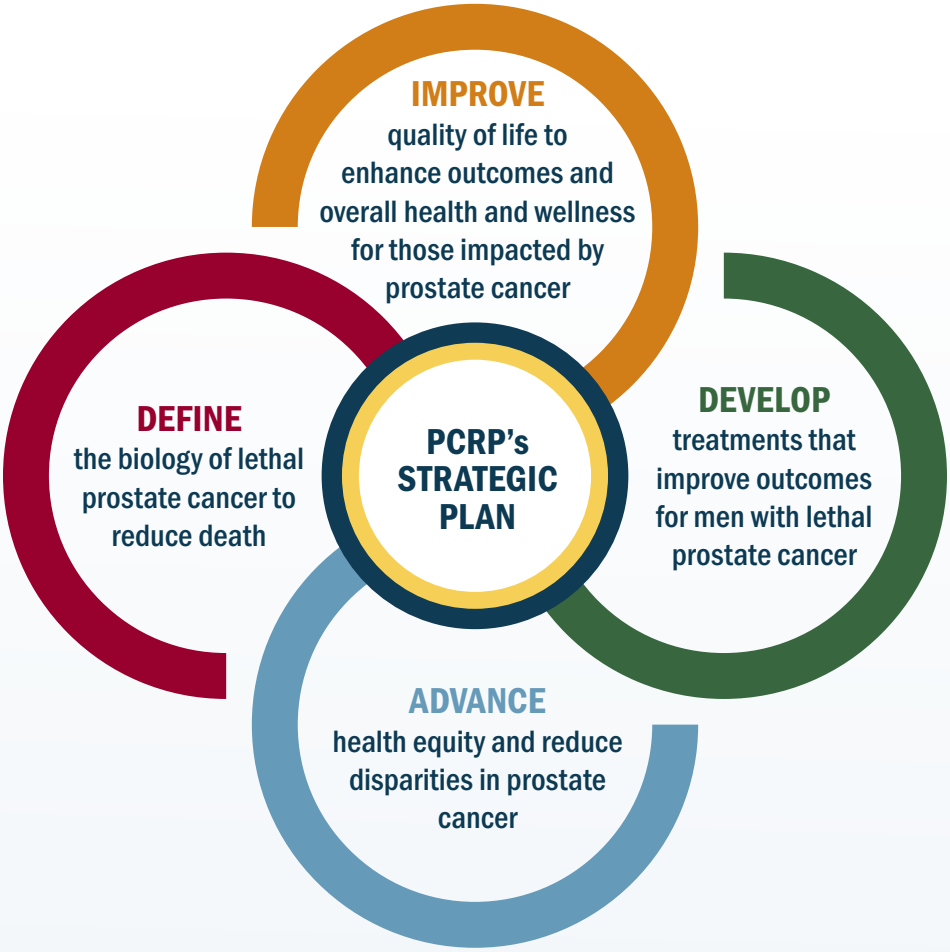
PCRP STRATEGIC DIRECTION

In 2018, the PCRP developed a Strategic Plan[1] that describes the program's 3- to 5-year plan for funding innovative and impactful ideas that benefit Service Members, Veterans, and the general public, ultimately leading to the elimination of death from prostate cancer. This document identifies the high-impact research goals that are most important to its stakeholders and provides a framework that can address those goals while remaining adaptable to changes in the medical research environment. The funding flexibility offered by the CDMRP enables the Programmatic Panel to make recommendations on defined research topics and projects for funding that directly address the PCRP's priority research areas. Each year, the PCRP analyzes its progress toward the strategic direction at the program's vision setting meeting. At that time, the PCRP reviews its investment strategy to ensure that it continues helping the program work toward accomplishing its Overarching Challenges and revises its strategy as needed.

[1] http://cdmrp.army.mil/pcrp/pdfs/PCRP%20Strategic%20Plan.pdf

OVERARCHING CHALLENGES

The PCRP remains focused on addressing the knowledge, research, and clinical gaps that continue to make prostate cancer a global health issue. As part of the PCRP's Strategic Plan, the program defined specific Overarching Challenges that are critical to providing further advancements that will impact current and future prostate cancer patients. Within this context, the PCRP is interested in supporting research that addresses specific gaps in prostate cancer research and clinical care, ***with an emphasis on investing in research that will benefit patients diagnosed with lethal prostate cancer or improve quality of life for men diagnosed with this disease***. All PCRP applicants are required to address at least one of the following FY21 Overarching Challenges in order to facilitate progress toward these goals and priorities as part of the PCRP's Strategic Plan:



Ken Pienta, Ph.D.

FY21–FY22 Programmatic Panel Chair, The Brady Urological Institute and the Department of Urology, Johns Hopkins School of Medicine

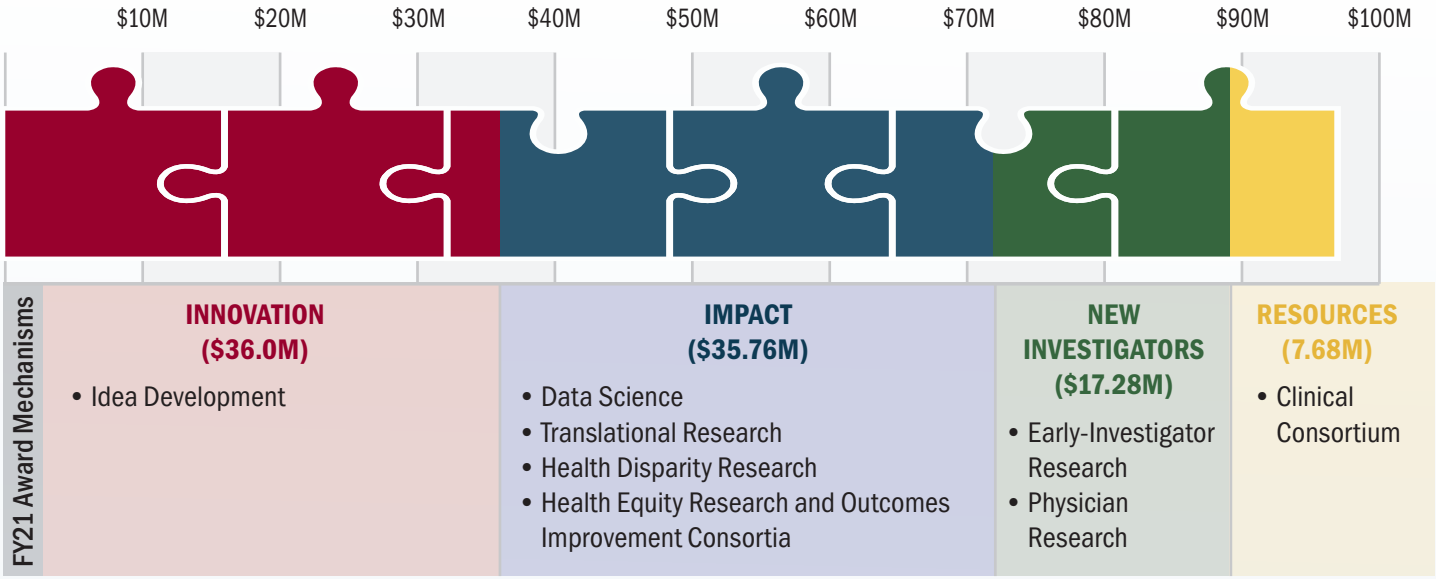
"The PCRP has transformed the research portfolio of the prostate cancer community over the last decade. Specifically, it has championed the funding of cutting-edge, 'out-of-the-box' ideas and projects without requiring large amounts of preliminary data. These idea awards, coupled with the funding of new investigators and trainees, has ensured a robust pipeline of new investigators to the prostate cancer battle."

INVESTMENT STRATEGY

The PCRP has traditionally offered a variety of funding mechanisms that help drive research forward from different approaches, all of which work together to address the Overarching Challenges and advance the mission of the PCRP. The FY21 PCRP Investment Strategy continues to offer award mechanisms that prioritize the following key areas:

- **INNOVATION:** Novel and potentially high-risk approaches to important research questions that could provide a significant impact and advance the field faster toward new advancements for patients
- **IMPACT:** Research with a high potential to make a significant impact for prostate cancer patients, in some cases in the near future
- **NEW INVESTIGATORS:** Support for career development of new prostate cancer research investigators who will become future leaders of the field and one day propose and discover new clinical advancements
- **RESOURCES:** Infrastructure support that brings together renowned scientific, clinical, and institutional resources for use by the prostate cancer research community to facilitate the translation of important findings from bench to bedside

Planned Investment Strategy for FY21



Carlos A. Casiano, Ph.D.

Professor and Associate Director, Center for Health Disparities and Molecular Medicine, Loma Linda University School of Medicine

"As a long-time PCRP reviewer and review panel chairperson, I have developed a deep appreciation for the commitment of this program to fund high-impact, translational research with great potential to reduce prostate cancer mortality. With PCRP funding, many young and established investigators have opened new areas of research, tested novel high-risk ideas, and developed cutting-edge technologies that have advanced tremendously the field of prostate cancer research. The PCRP is a superb program that is making a high impact in our fight against prostate cancer."

THE PROSTATE CANCER CLINICAL TRIALS CONSORTIUM

A NETWORK OF PROSTATE CANCER LEADERS FROM THE NATION'S TOP ACADEMIC MEDICAL CENTERS THAT IS UTILIZING A TEAM-BASED APPROACH TO DEVELOP DRUG CANDIDATES IN PHASES I AND I/2 THROUGH PHASE 3 CLINICAL TRIALS

For more information on products supported by the PCRP, see the clinical pipeline on page 25-31.

***Established in 2005** through the efforts of the PCRP and the Prostate Cancer Foundation to provide a pipeline of high-impact, novel therapeutic interventions that would decrease the impact of prostate cancer on patients' lives.*

*PCRP funding of **$59.2M** has resulted in treatment of more than **8,200** prostate cancer patients in **223** clinical trials, which have produced over **135** published manuscripts and contributed to the advancement of **21** agents to phase 3 testing.*

*Facilitated Food and Drug Administration (FDA) approval of **6 treatments** for prostate cancer patients, including the first androgen inhibitors for men with non-metastatic castration-resistant prostate cancer (mCRPC) through an expanded indication for **Xtandi®** and the launch of **Erleada®**.*

***Collaborative working group efforts** from the PCCTC have had an even broader impact on clinical trial design and patient care for prostate cancer, keeping the nation's premier prostate cancer clinical trials group at the forefront of research aimed at significantly impacting patients' lives.*

2008 / PCWG2*:
Results update 1999 recommendations and suggest new endpoints for mCRPC-focused clinical trials

2016 / PCWG3:
New recommendations provide framework for how best to use available agents in clinical practice

2019 / Germline Genetics WG*:
Identified practice patterns and barriers to germline testing for prostate cancer patients

2021 / PCWG4:
Plans to initiate group to reassess current outcome measures in post-COVID landscape

*Currently consists of **10** PCRP-funded and **70** affiliated clinical research sites distributed across the United States.*

*The nation's **premier prostate cancer clinical trials group** remains poised to make a significant impact on patients' lives by keeping the drug pipeline primed with promising novel agents.*

*Enrolled **2,800** patients for two major prostate cancer patient registries aimed at gathering patient-reported information to inform clinical practice and clinical trials: the International Registry to Improve Outcomes in Men with Advanced Prostate Cancer **("IRONMAN")**; and the Prostate Cancer Registry of Outcomes and Germline Mutations for Improved Survival and Treatment Effectiveness **("PROMISE")**.*

*PCWG = Prostate Cancer Working Group | WG = Working Group

IMPACT OF THE PCRP ON THE MILITARY HEALTH SYSTEM

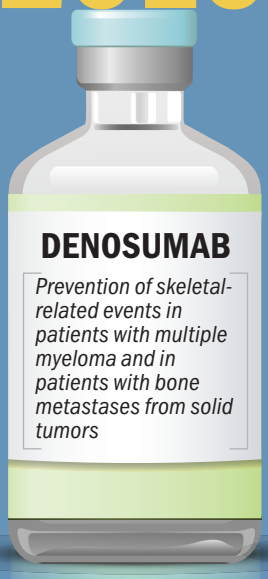
Prostate cancer
is a real threat to U.S. Service Members

80% of the **active duty population are men**

211,625
Active Service Members
and DOD beneficiaries treated for prostate cancer in MHS between 2010–2019*

PCRP funding, including support for the PCCTC, has been instrumental in the development and testing of a dozen different treatments and diagnostic tools that are now FDA-approved and commercially available. These advancements have impacted the clinical care received by Service Members, Veterans, as well as the general public, demonstrating the value and impact of the PCRP's support.

FDA APPROVAL **2010**



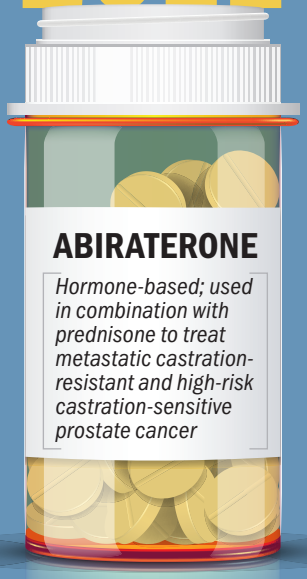
DENOSUMAB

Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors

7,094
prescriptions written**

740
patients within MHS

FDA APPROVAL **2011**



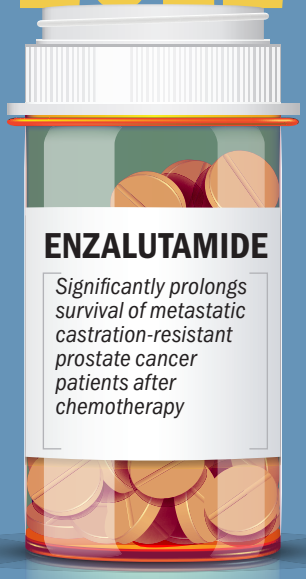
ABIRATERONE

Hormone-based; used in combination with prednisone to treat metastatic castration-resistant and high-risk castration-sensitive prostate cancer

54,244
prescriptions written**

5,478
patients within MHS

FDA APPROVAL **2012**



ENZALUTAMIDE

Significantly prolongs survival of metastatic castration-resistant prostate cancer patients after chemotherapy

41,099
prescriptions written**

4,436
patients within MHS

FDA APPROVAL **2018**

APALUTAMIDE

Used to treat patients with mCRPC and non-mCRPC

787
prescriptions written**

176
patients within MHS

*Data provided by the Armed Forces Health Surveillance Branch based on electronic records within Defense Medical Surveillance System.
** Prescriptions written to MHS patients since FDA approval. Source: Pharmacy Analytics Support Section.

YOUNG INVESTIGATOR AWARD SPOTLIGHT

For over a decade, the PCRP's Investment Strategy has prioritized investing in the innovative ideas proposed by young investigators. This allows the PCRP to foster a new generation of researchers who will bring new perspectives to the field and continue new research advances in the fight against prostate cancer (PCa) for many years to come. This investment has enabled these investigators to make significant contributions to prostate cancer research and patient care, and they are now helping to mentor the next generation of PCRP-funded new investigators who will further advance prostate cancer research efforts and identify new treatment approaches for patients. Below is a small snapshot of several PCRP new investigators and highlights of their contributions to prostate cancer research, along with their current PCRP-funded mentees.

FY00 NEW INVESTIGATOR AWARDEE

Folakemi Odedina, Ph.D.

Mayo Clinic Jacksonville

Award Outcomes: Developed a PCa screening model for African American (AA) men using predictors such as attitude, efficacy, behavior, and perceived susceptibility. This model outlines the "dos and don'ts" to design effective culturally-tailored educational tools to communicate to AA men the importance of PCa screening.

- *Recognized as a leader in the PCa disparity and health equity fields with multiple career achievement awards, her research focuses on predictors of health disparities and cost-effective, community-based behavioral interventions to improve the health of minority populations.*
- *Founder of the Epidemiology and Genomics Research Program supported Prostate Cancer Transatlantic Consortium (CaPTC).*

MENTEE

Motolani Ogunsanya

FY19 Early Investigator Awardee

Currrently developing a conceptual model using grounded theory in order to study quality of life of ethnically diverse AA PCa survivors.

6 *follow-on PCRP grants* **11** NIH/NCI grants totaling over $**15M**

Received Living Legend Award from the African Clinical Trial Summit (2017)

FY05 NEW INVESTIGATOR AWARDEE

Lorelei Mucci, M.P.H., Sc.D.

Harvard T.H. Chan School of Public Health

Award Outcomes: Using two large cohorts to predict tumor aggression and lethality at the time of diagnosis, molecular and physiological differences were identified between indolent and aggressive PCa, which can be utilized as predictive biomarkers for disease progression and inform patient-specific treatment decisions.

- *A leader in PCa population science research, she uses integrative molecular epidemiology among international cohorts to investigate cancer etiology, mortality, and survivorship.*
- *Currently co-Principal Investigator (PI) for the International Registry for Men with Advanced Prostate Cancer (IRONMAN) clinical trial that aims to understand which treatment and care practices deliver the best outcomes for men with advanced PCa.*

MENTEE

Claire Pernar

FY18 Early Investigator Awardee

Currently studying the longitudinal impact of treatment on cognitive function in men with advanced PCa.

1 *follow-on PCRP grant*

4 *follow-on NIH/NCI grants totaling* $**2.51M**

64 *senior author PCa publications*

300 *publications in total*

FY09 PHYSICIAN RESEARCH TRAINING AWARDEE

Felix Feng, M.D.

University of California, San Francisco

Award Outcomes: ETS gene fusions can promote oncogenic phenotypes through their association with DNA-PK and do not clinically impact radiation response, providing the foundation for designing novel targeted treatment strategies.

- *Currently co-PI of phase 2 "BALANCE" trial to study the effects of combining radiation with apalutamide in advanced recurrent PCa patients (NCT03371719).*
- *As the Vice Chair for Translational Research for the Department of Radiation Oncology, Dr. Feng's research is currently focused on translational research approaches for validating biomarkers associated with PCa treatment resistance.*

MENTEE

Lisa Chesner

FY20 Early Investigator Awardee

Currently studying the androgen receptor as a regulator of MHC Class I expression and immune evasion in advanced prostate cancer.

5 *follow-on PCRP grants totaling* **$6.5M** *in prostate cancer Research*

200 *PCa publications;* **5** *from PCRP awards*

FY10 POSTDOCTORAL TRAINING AWARDEE

Justin Drake, Ph.D.

University of Minnesota Medical School

Award Outcomes: Evaluation of rare mCRPC samples for changes in kinase phosphorylation revealed multiple druggable targets for further clinical evaluation, including SRC, EGFR, RET, ALK, and MAPK1/3.

- *Current research efforts blend basic and translational research approaches to understand the role of kinase signaling and identify therapeutic targets that lead to progression of disease toward castration-resistant PCa and neuroendocrine PCa.*
- *He has mentored over 20 junior scientists, including two PCRP new investigator awardees, Helena VanDeusen (FY18 recipient) and Zoi Sychev (FY19 recipient), and is a Preceptor in the Medical Scientist Training Program, guiding more physicians and scientists into prostate cancer research.*

MENTEE

Halena VanDeusen

FY18 Early Investigator Awardee

Currently working to elucidate the mechanism of RET kinase activity in neuroendocrine PCa.

3 *follow-on PCRP grants totaling* **$1.6M** *in PCa Research*

31 *PCa publications;* **5** *from PCRP award*

FY12 PHYSICIAN RESEARCH TRAINING AWARDEE

Himisha Beltran, M.D.

Dana-Farber Cancer Institute

Award Outcomes: Results of integrative genomic and epigenomic analyses of metastatic tumors in neuroendocrine phenotypes led to the identification of novel drivers of treatment resistors and potential biomarkers to determine patients who are less likely to respond to conventional AR therapy and should be selected for alternative neuroendocrine prostate cancer (NEPC)-directed approaches.

- *An established leader in PCa translational research, aiming to bring novel therapeutics to overcome PCa treatment resistance to patients.*
- *Principal Investigator of a "Phase 2 Trial of MLN8237, an Aurora A Inhibitor, in Patients with Metastatic Castrate-Resistant and Neuroendocrine Prostate Cancer Award" (NCT01799278), resulting from PCRP research.*

MENTEE

Sheng-Yu Ku

FY19 Early Investigator Awardee

Investigating crosstalk between Notch signaling and lineage determining transcriptional factors that drive neuroendocrine differentiation in advanced PCa.

3 *follow-on PCRP grants totaling* **$4.1M** *in PCa Research*

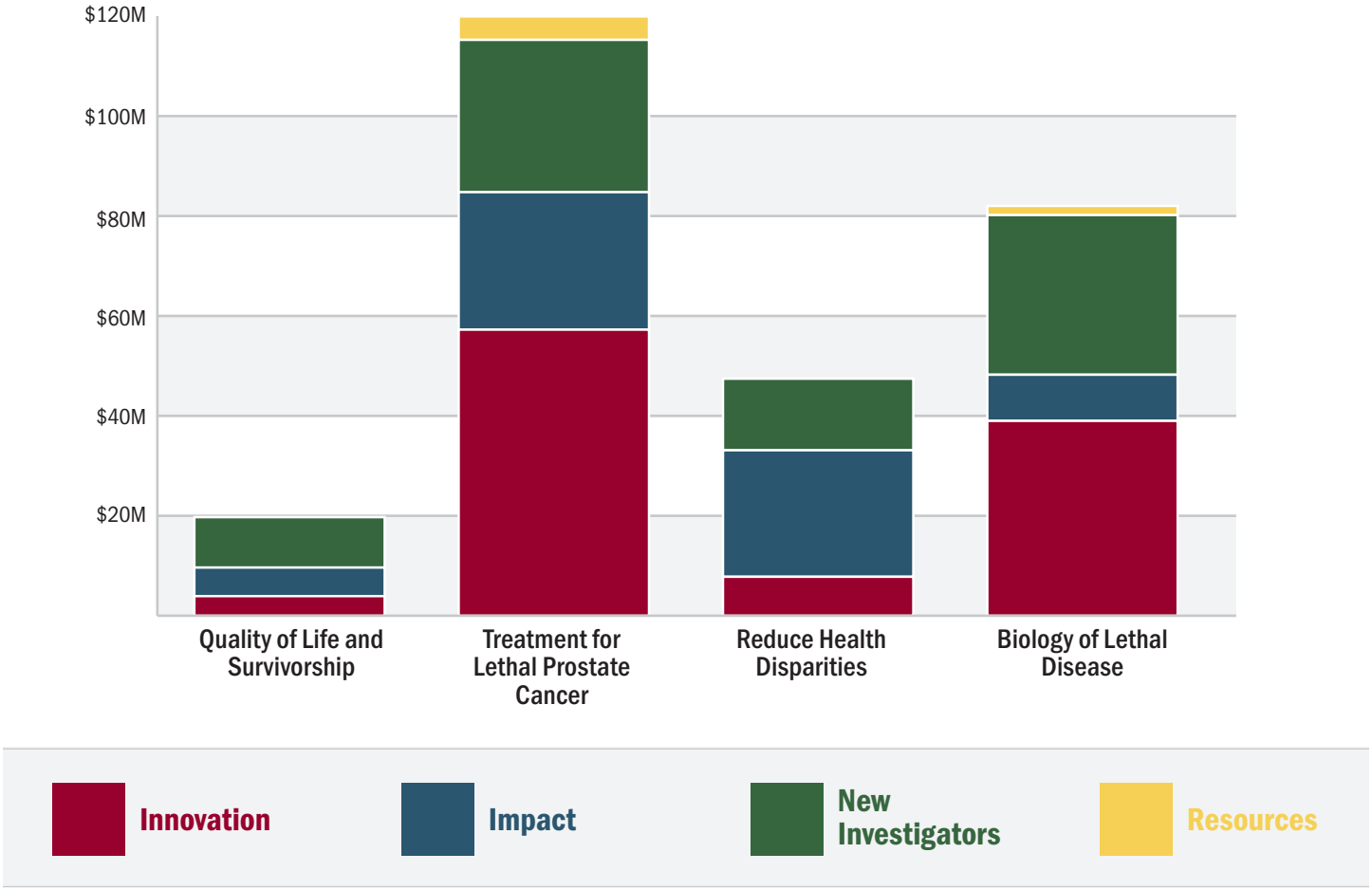
largest *tissue biopositories of NEPC, and have led to* **additional funding**

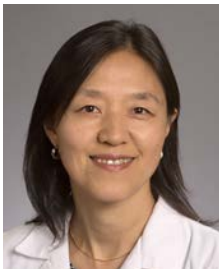
PCRP-FUNDED RESEARCH

IN ORDER TO ACHIEVE ITS MISSION TO CONQUER PROSTATE CANCER, THE PCRP CRAFTS ITS ANNUAL INVESTMENT STRATEGY AND PRIORITIZES RESEARCH THAT BEST ALIGNS WITH THE CURRENT STRATEGIC GOALS (PAGE 6-7).

The PCRP requires all applicants to address at least one Overarching Challenge to ensure it is funding research that addresses an unmet need in prostate cancer research or clinical care. The graph below represents the program's investment since crafting the Strategic Plan in 2018. While not exhaustive, the following research highlights on pages 13-24 feature a small subset of projects in the PCRP portfolio that have made great strides and progress towards addressing the identified Overarching Challenge.

PCRP Investment in the Overarching Challenges from FY18–FY20 ($269.1M)





PRESERVING SEXUAL FUNCTION IN MEN UNDERGOING RADIATION TREATMENT FOR PROSTATE CANCER

Tian Liu, Ph.D. and **Ashesh Jani, M.D.,** Emory University

One of the most common complications experienced by men undergoing radiotherapy for prostate cancer is decreased sexual function. Radiation can damage blood vessels and nerves surrounding the prostate, resulting in erectile dysfunction over time and highlighting the need for new nerve-sparing therapies. Some researchers theorize that this side effect could be due to injury to the neurovascular bundles (NVB) surrounding the prostate, which are difficult to visualize with current imaging techniques. Because sexual dysfunction can occur in up to 50% of men undergoing radiotherapy, there is a need for non-invasive imaging techniques that could spare the NVB, thereby increasing quality of life for prostate cancer patients.

With support from an FY16 Idea Development Award (Established Investigator – Partnering PI Option), Dr. Tian Liu and Dr. Ashesh Jani at Emory University are developing and testing a multimodality imaging platform to measure neurovascular bundle (NVB) injury caused by radiation. Dr. Liu's team is currently developing the technology, which will combine magnetic resonance imaging (MRI) and ultrasound to measure radiation-related NVB injury (Figure 1). Dr. Jani has been leading a clinical study to validate the results of the platform and correlate findings with standard clinical endpoints to evaluate erectile dysfunction. The team will also conduct a feasibility study to investigate the ability of this novel technology to improve sexual potency through NVB-sparing radiotherapy.

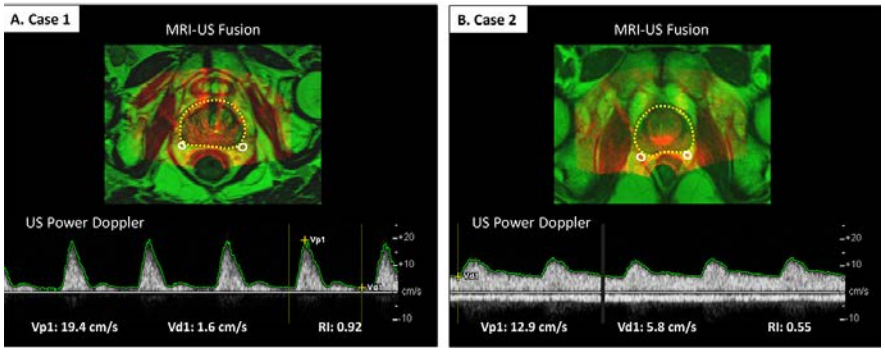


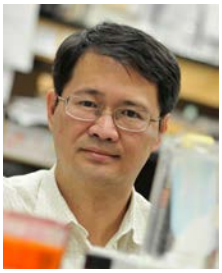
Figure 1. Multimodality MRI-US NVB imaging platform. Case 1: Power Doppler shows NVB blood flow of 59-year-old patient with normal sexual function. Case 2: Lower NVB blood flow in 61-year-old patient with erectile dysfunction.

To date, the research team has created a unique prostate phantom with NVB components for preclinical testing and develop a method to analyze Doppler waveforms obtained from ultrasound imaging. This Doppler technology provided more accurate blood flow measurements surrounding the prostate. During radiotherapy treatment planning, clinicians use a process called segmentation to accurately determine prostate boundaries to localize radiotherapy and spare healthy tissues. To overcome the time-consuming process of manual segmentation of the prostate during transrectal ultrasound (TRUS), Co-Investigator, Dr. Xiaofeng Yang, and the team developed a multidirectional deep-learning method to automatically segment the prostate during TRUS-guided radiotherapy, which was published in *Medical Physics*. In addition, the team developed a weakly supervised learning-based MRI-TRUS image registration that which could quickly fuse MRI with TRUS to help the NVB localization.[2] A total of 28 subjects have been recruited for the clinical study, 18 (64%) of which are AA men to provide a more diverse set of patient outcomes. Additionally, an imaging and outcomes database has been developed to correlate the team's images with patient-reported outcomes and clinical data, in the hope of further optimizing and validating the platform in patients.

Results from this study could allow physicians to prevent NVB injury due to radiotherapy and potentially adjust radiation dosage during radiotherapy treatment planning. This work could also lead to new nerve-sparing therapies for prostate cancer patients that would preserve sexual function and increase quality of life.

Additional Information:

Public and Technical Abstracts: Multimodality Imaging Platform for Neurovascular Bundle Sparing Prostate Radiotherapy to Preserve Sexual Function



ARTIFICIAL LYMPH NODE: A TRAP TO STUDY AND FIGHT PROSTATE CANCER

Liping Tang, Ph.D., University of Texas at Arlington

Spreading of prostate cancer to the lymph nodes is the hallmark of cancer metastasis, which has a significant negative effect on patient survival. Unfortunately, the mechanism(s) governing prostate cancer lymph node metastasis is not completely understood, and there is no specific treatment for reducing such metastasis. Since lymph nodes are small organs spread out all over the body, investigating their mechanisms is very difficult. With support from an FY13 Idea Development Award, Dr. Liping Tang and his interdisciplinary team of investigators developed a lymph node device that can be used for studying lymph node and cancer interactions.

Dr. Tang and his colleagues first discovered that highly metastatic prostate cancer, but not low metastatic prostate cancer, would cause lymph nodes to swell. By comparing the cellular and protein components between swollen and naïve lymph nodes, the research team found that the invasion of highly metastatic prostate cancer cells, but not low-metastatic cancer cells, would activate lymph node T cells to produce several key chemokines that play a role in cancer metastasis. Based on these results, the investigative team built a T cells-seeded lymph node device in order to more closely examine cancer and T cell interactions. Results show that the lymph node device can trigger differential responses to both highly metastatic and low-metastatic prostate cancer. For example, placing the lymph node device near the primary tumor in animals was shown to reduce lymph node metastasis by actively capturing circulating prostate cancer cells.

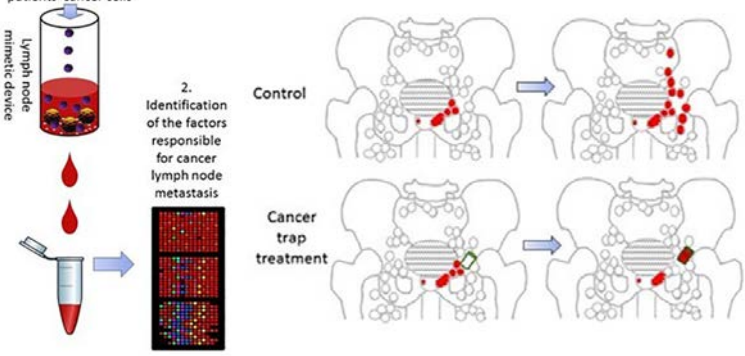


Figure 2: Schematic illustration of cancer trap for intercepting prostate cancer cells from lymph node metastasis.

Dr. Tang is currently engineering a new lymph node device for both metastatic cancer diagnosis in vitro and prostate cancer lymph node metastasis treatment in vivo. For in vitro diagnosis, uncharacterized prostate cancer cells can be placed in the 3D lymph node device. By analyzing the "lymph fluid" from the device using protein array technology, he can determine whether unknown cancer cells have metastatic potential. In addition, based on the identified biomolecules, a specific and personalized treatment for reducing lymph node metastasis may be developed. For in vivo treatment, a 3D implantable lymph node device will be made for easy implantation nearby the primary tumor. Such an implant can serve as a "cancer trap" for capturing metastatic prostate cancer cells and reducing lymph node metastasis.

Additional Information:

Public and Technical Abstracts: Tissue-Engineered Constructs for Investigating the Effect of Lymph Node Microenvironment on Prostate Cancer Metastasis

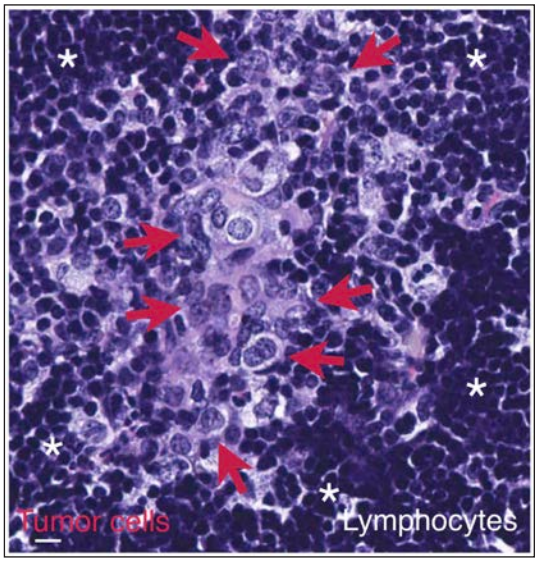
USING A NOVEL GENETICALLY ENGINEERED MOUSE MODEL TO IDENTIFY NEW DRUG TARGETS FOR TREATMENT-RESISTANT METASTATIC PROSTATE CANCER

Lloyd Trotman, Ph.D., Cold Spring Harbor Laboratory

The standard of care approach for treating metastatic disease utilizes anti-hormone therapy to shut down the main driving pathway of the cancer cells. Unfortunately, cancer cells usually adapt to this altered environment, and they become resistant to this form of therapy. With approximately 32,000 men in the U.S. failing to respond to available therapies and dying of prostate cancer each year, it is important to find new options for treating metastatic disease. The focus of Dr. Lloyd Trotman's research at the Cold Spring Harbor Laboratory is to understand the mechanisms driving human prostate cancer in its most lethal, metastatic form in order to identify novel drug targets for these patients.

In order to properly study prostate cancer metastasis, Dr. Trotman and his research team sought to develop a mouse model that recapitulates human disease but in a much accelerated time frame. With support from an FY13 Idea Development Award, they developed a new genetically engineered mouse model called RapidCaP. This mouse model accurately recreates the journey from a native prostate tumor to metastasis in an immune competent animal.

The MYC gene is a known oncogene and driver of many cancers, including prostate cancer, where it is often highly expressed in metastatic disease. Unfortunately, there has been little success in targeting MYC with drugs so far. Using the RapidCaP mouse model they developed, Dr. Trotman and his team have discovered that MYC depends on an enzyme called PHLPP2 (pronounced FLIP-2), which protects MYC from degradation. This finding has revealed a novel approach to target MYC indirectly by developing PHLPP2 inhibitors.



The research team at Cold Spring Harbor is continuing to make advances in understanding basic fundamentals of metastasis. Since the early 2000s, they have made huge strides in understanding prostate tumors by comparing human patient samples with those from genetically engineered mice. Through their PCRP-funded work, they have identified PHLPP2 as a druggable target of MYC-driven prostate cancer and are currently testing how to best inhibit PHLPP2 in vivo. Furthermore, the team continues to use the RapidCap mouse model to identify additional novel drug targets in hopes to develop new therapies for men with treatment-resistant metastatic prostate cancer.

Additional Information:
RapidCaP, a Novel GEM Model to Fight Treatment-Resistant Metastatic Prostate Cancer

Shawn Lupold, Ph.D.

Scientific Peer Reviewer, Johns Hopkins School of Medicine

"As a prostate cancer research scientist, it is always an honor to serve on PCRP peer review panels. There is a special camaraderie that forms between scientist reviewers, consumer reviewers, and review officers over those few days. When the reviewers gather the first day of the review, there is a collective sense of duty for rigorous and fair review that focuses on disease impact and the overarching goals of the program. This is an outstanding resource for prostate cancer researchers, patients, and their families."

SYNERGISTIC ACTION OF FOXP3 AND TSC1 PATHWAYS IN PROSTATE CANCER PROGRESSION

Lizhong Wang, Ph.D., University of Alabama, Birmingham

Prostate cancer is the most common type of cancer in men in the U.S., and more than 80% of men will develop prostate cancer by the time they are 80 years old. In the majority of cases, prostate tumors are indolent and slow-growing, although some become more aggressive and ultimately lethal. The mechanisms within prostate cells that control progression of the tumors to aggressive disease are not fully understood. Identification of these mechanisms could lead to the development of improved treatment options for aggressive prostate cancer.

To help understand the molecular mechanism of progression from indolent to aggressive prostate cancer, Dr. Lizhong Wang and his research team at the University of Alabama at Birmingham have demonstrated that Foxp3, previously identified as X-linked prostate tumor suppressor protein, and Tsc1, an essential protein component of the PI3K/Akt/Tsc1/2/mTOR signaling pathway, both inhibit tumor progression in prostate cancer. Additionally, they found that deletions of TSC1 are frequently accompanied by FOXP3 defects. With support from an FY13 Idea Development Award – New Investigator, they examined potential crosstalk between these two proteins and how that leads to suppression of prostate cancer tumor progression.

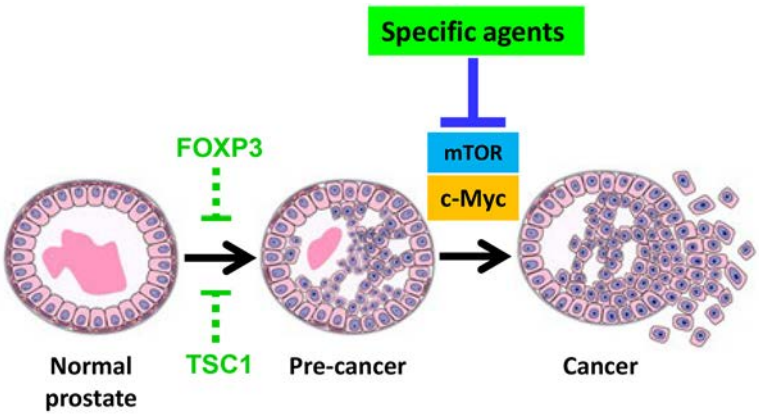


Figure 3: The cooperation of Foxp3 and Tsc1 proteins inhibits c-Myc activation and tumor progression in prostate cancer. The green dotted lines indicate where FOXP3 and TSC1 proteins normally block tumor formation, and the blue line indicates how chemicals that inhibit both mTOR and c-Myc prevent progression to prostate cancer.

Through comprehensive analyses performed using both in vitro and clinically relevant in vivo models, Dr. Wang and his team found that TSC1 and FOXP3 act synergistically to suppress tumor progression through inhibition of two other proteins, mTOR and c-MYC, which promote the growth of tumor cells. Many candidate anti-tumor drugs, such as the mTOR inhibitor rapamycin, have not been successful in prostate cancer clinical trials to date; it is believed that persistent activation of c-MYC may be the cause of resistance to these therapies. Dr. Wang's group is therefore testing the anti-tumor effects of combining mTOR and c-MYC inhibitors using preclinical mouse models of prostate cancer that were developed in their laboratory to see whether the combination treatment will overcome the resistance to mTOR inhibitors commonly seen in prostate cancer.

By providing better understanding of one mechanism that enables tumor progression from indolent to aggressive prostate cancer, Dr. Wang has also provided evidence that further work to identify pharmaceutical drugs that target both mTOR and c-MYC may be a new therapeutic approach that will help make prostate cancer cells more responsive to mTOR inhibitors and ultimately enable clinicians to provide more effective treatment options for patients with aggressive prostate cancer.

Additional Information:

Synergistic Action of FOXP3 and TSC1 Pathways During Tumor Progression

INVESTIGATING RACIAL DIFFERENCES IN THE FINANCIAL IMPACT OF PROSTATE CANCER

James Mohler, M.D., Roswell Park Comprehensive Cancer Center

The North Carolina–Louisiana Prostate Cancer Project (PCaP), led by Drs. James Mohler (Roswell Park) and Jeannette Bensen (University of North Carolina at Chapel Hill), was initially funded by the PCRP in FY02 and represents the largest population-based study of newly diagnosed prostate cancer in AA and Caucasian American (CA) men ever conducted, with 2,258 participants. The study published results in 2017 that demonstrated that racial differences in prostate cancer survival appear to originate more from a weak relationship of AA men with the American healthcare system, and poverty presents a significant obstacle to effective medical care for AA men compared to CA men. Thus, while FDA approval of new treatments (e.g., immunotherapy, anti-androgens, radiopharmaceuticals, and chemotherapies) are extending the lives of patients with mCRPC, the long-lasting side effects and large expense of these treatments places a significant financial burden and stress on prostate cancer patients and their families and may contribute to disparate outcomes in AA prostate cancer patients.

In FY16, Dr. Mohler was awarded a Health Disparity Research Award to obtain 10-year follow-up data on the original group of prostate cancer patients from the PCaP and their caregivers. A critical goal of the project is to better understand the financial impact of prostate cancer treatment on patient survival and quality of life in both AA and CA men and to develop interventions to reduce the financial burdens and stress associated with a prostate cancer diagnosis. Dr. Mohler's collaborators, including Dr. Ed Peters and his team at Louisiana State University Health Sciences Center School of Public Health, are conducting surveys of PCaP participants and their caregivers through telephone, paper, and web-based questionnaires. Of the 1,331 living patients from the original group of PCaP patients, 561 (42% participation rate) have completed the questionnaires, and the data have been entered and quality-checked. A very preliminary analysis compared financial distress in 194 patients by site (North Carolina, n= 76 versus Louisiana, n= 118) and by race (AA, n= 53 versus CA, n= 141), and the initial results showed slightly higher financial toxicity for AA respondents regardless of location (Figure 1).

Through this award, Dr. Mohler and his team are attempting to obtain electronic medical data using new methodology in both states. In Lousiana, the Surveillance, Epidemiology, and End Results (SEER) Program provides vital status and recurrence data that is enhanced through the Patient-Centered Outcomes Research Institute (PCORI)-supported Louisiana REACHnet that accesses data from clinical practices, health care systems and insurance claims. In North Carolina, the University of North Carolina's Cancer Information and Population Resource has linkages to the North Carolina Central Cancer Registry and administrative and health insurance claims data from private payers, as well as Medicare and Medicaid. The necessary agreements are almost in place to allow electronic collection of information on the level of insurance coverage over the follow-up period, prostate cancer-specific treatments, medications, oncologic status, prostate-specific antigen (PSA) frequency and side effects, which will be used to construct "OncoGraphs" on all participants. Some missing data will continue to be collected from living PCaP participants and their physicians in North Carolina and Louisiana. This rich dataset will provide valuable insight into the financial stress incurred by AA and CA prostate cancer patients and their families, as well as highlight the socioeconomic disparities faced by those living with the disease. Furthermore, the dataset will provide a picture of the level of insurance coverage and level of care during the follow-up period for each participant, which may highlight further racial disparities during long-term prostate cancer follow-up.

Additional Information:

Public and Technical Abstracts: Racial Differences in Financial Impact of Prostate Cancer Treatment and Outcome

INVESTIGATING THE MOLECULAR DIFFERENCES LEADING TO RACIAL HEALTH DISPARITIES IN PROSTATE CANCER PATIENTS

Nallasivam Palanisamy, Ph.D., Henry Ford Health System

AA men are 50% more likely to develop prostate cancer and are twice as likely to succumb to the disease as men of other races. Although this disparity may in part be attributed to socioeconomic factors and access to resources, there is an unmet research need to investigate the genetic differences between AA and CA prostate cancer. The prevalence of common molecular biomarkers for prostate cancer is largely unexplored in AA men, highlighting the need to apply innovative molecular approaches to understand the impact of prostate cancer biology on racial disparities.

Funded by an FY15 Health Disparity Research Award, Dr. Nallasivam Palanisamy investigated the genetic differences between AA and CA prostate cancer patient samples, with the ultimate goal of discovering new biomarkers specific to AA prostate cancer. His approach was to screen tissues from whole mount radical prostatectomies, rather than systemic sampling of the primary tumor, to assess the expression pattern of prevalent prostate cancer biomarkers: ERG, SPINK1, ETV1, ETV4, ETV5, and PTEN. A total of 981 samples were utilized across the study – 525 from CA patients, 409 from AA patients, and 47 from patients of other racial backgrounds. Dr. Palanisamy's team found that ERG overexpression was more prevalent in CA patients than AA patients, while SPINK1 was more commonly overexpressed in AA patients. Because the entire prostate tissue was examined, rather than only the primary tumor, it was found that 260 samples were positive for more than one marker. Of the 838 samples investigated for ERG and SPINK1, 18% were ERG+/SPINK1+, which was also found to be more prevalent in AA patients. Detailed statistical analyses examining the link between the molecular heterogeneity of these tumors and disease progression are currently underway.

The research team also investigated the relationship between these molecular signatures and clinical data within each racial group. They found that ERG overexpression correlated with a lower Gleason grade in CA patients and SPINK1 overexpression was associated with a lower Gleason grade in AA patients. They also assessed correlations to tumor stage, tumor volume, and age, and statistical analyses are underway. Importantly, this work sets the stage for targeted diagnostic and treatment approaches and highlights the importance of recognizing the differences in the biology of prostate cancer that could provide insight into racial disparities.

LTC Clarence Luckett

Consumer Peer Reviewer, Georgia Prostate Cancer Coalition Board Member

"Serving as a consumer reviewer on the scientific review panels is absolutely fulfilling! The PCRP allows me to continue my personal and professional growth with prostate cancer, which provides a viable and reliable voice for our non-profit organization—the Georgia Prostate Cancer Coalition (GPCC). The more immersed I am in the prostate research, the more GPCC's advocacy can serve the community here in Georgia. Most importantly, the PCRP has made a significant impact not only for me, but also for the broader prostate cancer community. I hope that the PCRP continues to be funded until prostate cancer no longer exists for men! HooaH!"

REAL-TIME VISUALIZATION OF MICROSCOPIC RESIDUAL PROSTATE CANCER AT THE TIME OF RADICAL PROSTATECTOMY

Mekhail Anwar, M.D. Ph.D., Department of Radiation Oncology, University of California, San Francisco

Approximately 20%-40% of all prostate cancer patients who have undergone radical prostatectomy eventually present with biochemical recurrence that, if unsuccessfully treated, will result in lethal disease. Standard surgical practice includes fully removing the prostate, followed by pathological evaluation of the tumor to assess the extent of disease. However, there are currently no intraoperative detection methods to ensure that microscopic cancer cells, which might be eliminated by post-operative radiation therapy, have effectively been removed after surgery, underscoring the need for more precise techniques for imaging the tumor prior to radical prostatectomy to reduce the chances of a patient developing lethal prostate cancer.

With funding from an FY14 Physician Research Training Award, Dr. Mekhail Anwar developed PRECISION (*Prostate Resection EnhanCed vIa ultraSensitive Intraoperative Optical Navigation*) through design and fabrication of a microfabricated fluorescent imager to detect microscopic residual disease (MRD) at the time of surgery. He and his research team at the University of California, San Francisco (UCSF) used a fluorescent-conjugated antibody that is injected 48 hours before surgery and targets prostate-specific membrane antigen (PSMA), a previously validated marker of prostate cancer. The goal of the project was to develop a chip-scale imager capable of direct integration with a laparoscopic or robotic drop-in probe that can be placed directly onto the patient tumor bed to illuminate as few as 200 microscopic prostate cancer cells in real time. The research team hopes that this technique could be used in an intraoperative setting, at the time of the radical prostatectomy, to ensure that the tumor has been completely excised. This work will also enhance understanding of how MRD affects clinical outcomes in prostate cancer patients.

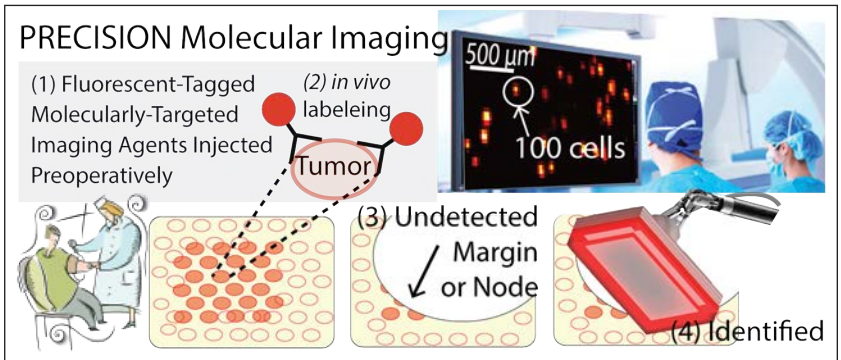


Figure 4: Envisioned Workflow Fluorescently-tagged antibodies are injected preoperatively, labeling tumor cells in vivo. Resection is performed and PRECISION is manipulated by a robotic surgical grasper, examining the surface for residual disease. The real-time (<0.01s) images are projected onto a monitor and automated image recognition software identifies, quantifies, and maps, the tumor cells seen.

Dr. Anwar conducted in vitro experiments to optimize this novel technology by using LNCaP, a type of PSMA overexpressing prostate cancer cell cultured with an anti-PSMA conjugate to directly quantify the number of molecules bound per cell. This process was then validated in formalin-fixed tissue samples from human prostate cancer biopsies. Dr. Anwar used the antibody, GCP-05, conjugated to Alexa Fluor 700, which recognizes extracellular PSMA with high affinity for optimal binding. Using PSMA-GCP-05 Alexa Fluor 700, which incorporates the target, antibody, and fluorophore, the imager was able to detect as few as 100 prostate cancer cells in vitro. The imager was also tested in vivo in a small animal model of prostate cancer to validate the functionality and sensitivity of the system. Results showed that the PSMA tumor labeled with the PSMA-GCP-05 Alexa Flour 700 was successfully visualized starting at 5 hours and up to 73 hours.

Dr. Anwar obtained a provisional patent for this new technology and is now currently working with Dr. Peter Carroll and Dr. Matt Cooperberg at UCSF to ensure that this new imager can be fully integrated with existing surgical procedures and tools to maximize its clinical utility. This work supported by the PCRP has provided the proof of concept for future clinical trials and, if successful, could result in a real-time imaging platform capable of ensuring complete resection of MRD during radical prostatectomy to minimize recurrence and improve outcomes in prostate cancer patients.

Additional Information:

Public and Technical Abstract: Identification and Treatment of Microscopic Residual and Recurrent Disease in Prostate Cancer Using in Vivo Microfabricated Sensors and Targeted Biologics

FIRST-IN-CLASS ANTI-sMIC IMMUNOTHERAPY ANTIBODY THERAPY TO TARGET PROSTATE CANCER METASTASIS

Jennifer Wu, Ph.D., Northwestern University

Dr. Jennifer Wu and her team have been investigating the mechanisms driving prostate cancer progression and developing novel treatments and models to combat metastasis. With the support of an FY05 Idea Development Award, she discovered that in advanced stages of prostate cancer, the cancer cells could not only escape immune system surveillance, but could also disable the immune system response.

The underlying mechanisms for these events came from the oncogenic stress-induced molecule called "MIC." In healthy cells, MIC is not expressed on cell surfaces. However, during cancer development, and even at very early stages, prostate cells start to express MIC. The primary function of MIC is to "flag down" the immune cells, particularly the natural killer and cytotoxic T cells, to initiate their response in fighting cancer cells. However, in stages of advanced prostate cancer, the cancer cells have "chopped off" or eliminated the ability of MIC to "flag down" the immune cells. Hence, the cancer cells are able to bypass immune surveillance and roam free. More detrimentally, cancer cells release a soluble form of MIC, called sMIC, which shuts down the immune system and thus allows for the cancer cells to "dodge" immune cells. These mechanisms may explain the non-responsiveness to immunotherapy in patients with advanced prostate cancer.

To address this problem, Dr. Wu developed a first-in-class monoclonal antibody to target sMIC. In preclinical models, the antibody has been found to "revive" immune system function and eliminate prostate cancer metastasis. When administered solo, the antibody has already shown promise in controlling metastasis of cancer cells, and even in non-responders to immunotherapy. When administered in combination with an immune checkpoint blockade, a synergistic anti-tumor effect occurs where both agents work to restore immune function.

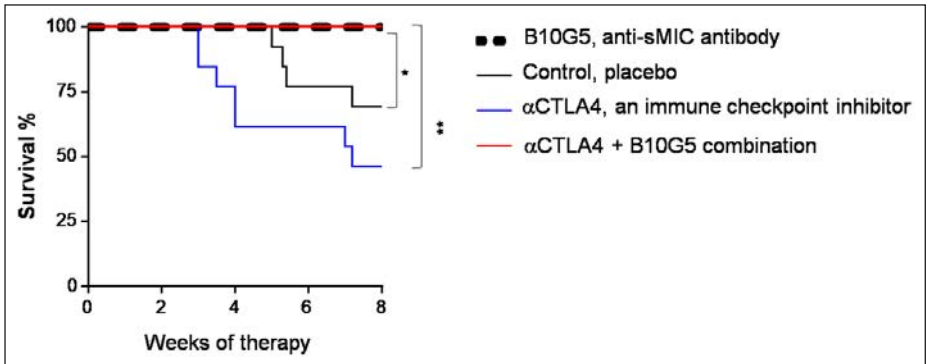


Figure 5: A survival curve showing that the combination therapy of B10G5 and anti-CTLA4 significantly re-sensitizes prostate tumors to anti-CTLA4 therapy and improves survival. Note that anti-CTLA4 is a FDA-approved immunotherapy for melanoma.

Dr. Wu and her colleagues are working toward bringing this anti-sMIC antibody from preclinical to clinical use in humans and plan to investigate how to use the antibody to tackle neuroendocrine prostate cancer, the most lethal type prostate cancer. As a first step in addressing human use of the antibody, Dr. Wu has created a "humanized MIC" prostate cancer mouse model, which consists of the actual MIC molecule found in humans, as mice do not naturally express this molecule. With the support from an FY14 Idea Development Award – Established Investigator, Dr. Wu has been able to more accurately study the interaction between prostate cancer cells and the immune system. Through collaboration with the pharmaceutical industry, Dr. Wu hopes to further validate the efficacy of therapy of her antibody and bring her design closer to human use in the near future.

Additional Information:

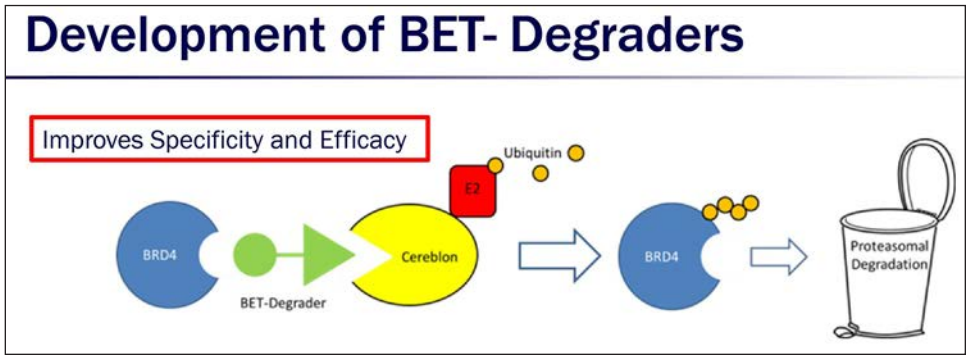
Public and Technical Abstracts: Enhancing Anti-CTLA4 Immunology Therapy for Prostate Cancer with Cotargeting Soluble NKG2D

BET BROMODOMAIN DEGRADERS FOR THE TREATMENT OF METASTATIC PROSTATE CANCER

Steven Kregel, Ph.D., University of Michigan

The standard treatment for advanced, metastatic prostate cancer involves blocking the body's production of androgens by targeting the androgen receptor (AR), which drives the growth of prostate cancer cells. While this treatment option is initially successful, most acquire resistance and ultimately progress to lethal disease. Consequently, there is a critical need to develop drugs targeting other proteins involved in AR activity rather than AR directly. One protein group that represents a good therapeutic target is called bromodomain and extraterminal (BET) containing proteins, which interact with AR to drive prostate cancer progression to metastatic disease. There have been great efforts to target BET proteins by blocking the action of these proteins, although many of these drugs are not specific, have off target side effects, and often lead to rapid drug resistance. Dr. Steven Kregel and his research team at the University of Michigan have aimed to develop molecules that target BET proteins through a different mechanism, called proteosomal degradation, in which the compound tags the BET protein for the body's own recycling.

With funding from an FY16 PCRP Early Investigator Award and under the mentorship of Dr. Arul Chinnaiyan, Dr. Kregel has tested and characterized several candidate inhibitors in preclinical prostate cancer models. Through this work, he has identified the BET degrader, dBET-3 (ZBC-260), as the lead candidate compound. He first tested this compound in a panel of prostate cancer cell lines and found that it effectively degraded BET proteins as well as another cancer-driving gene called MYC. Through patient-derived tumor mouse models, he discovered that mice treated with dBET-3 had significantly smaller, slower-growing tumors than the control group. Importantly, the BET degrader was effective at inhibiting prostate cancer growth at lower concentrations than BET inhibitors both in vitro and in vivo.



This research group is continuing to test the dBET-3 compound in preclinical models of drug-tolerability and dosage in preparation for a phase 1 clinical trial in prostate cancer patients. Additional versions of the drug to improve its bioavailability and cancer cell-specific targeting are also being developed, such as the newly characterized QCA570, as well as selective inhibitors of individual BET proteins to prevent potential tissue-specific side effects. This group now has multiple modifications of the lead compound, dBET-3, being produced for phase 1 clinical trials. Ultimately, they hope to advance this work into the clinic for the treatment of metastatic prostate cancer.

Additional Information:

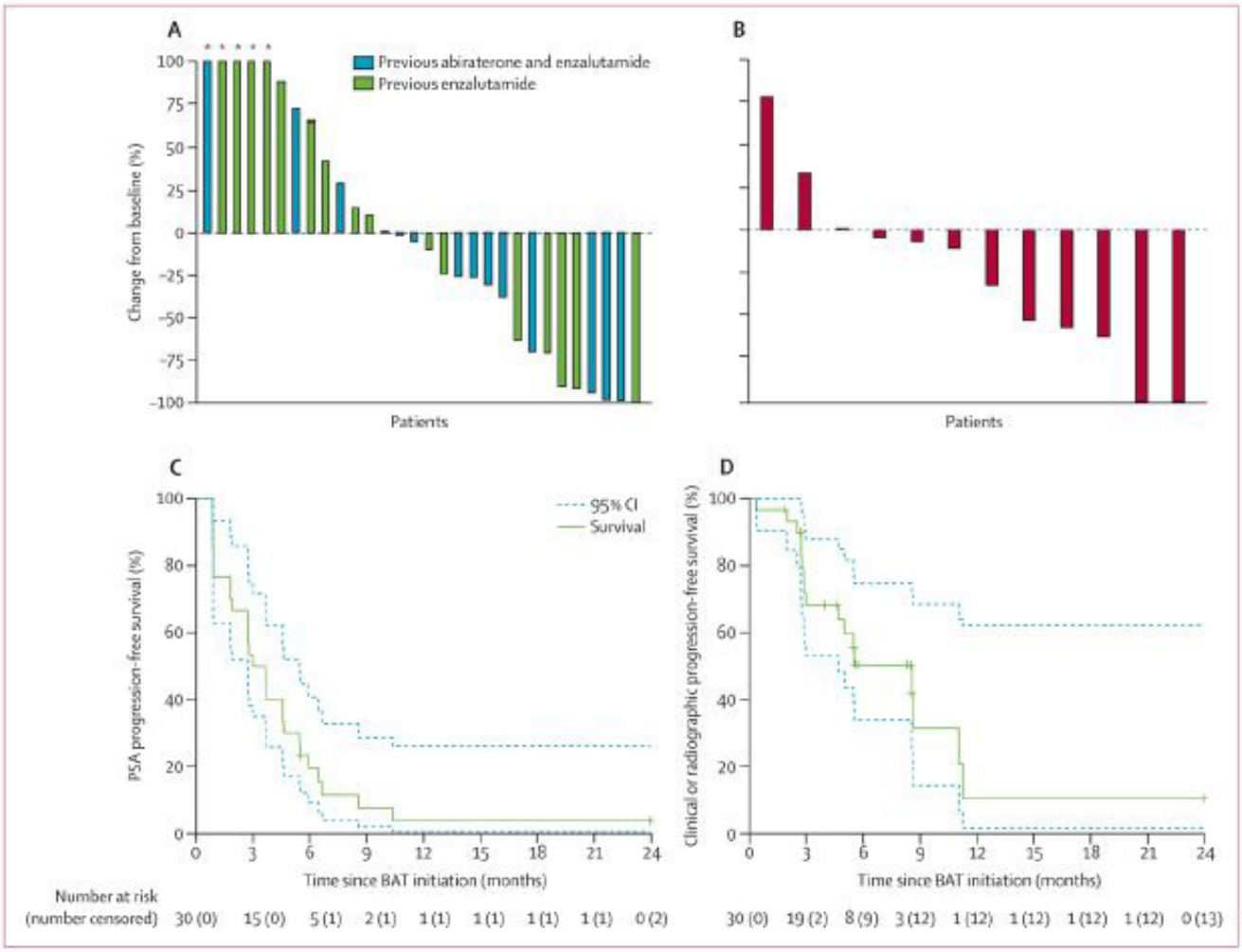
Functional and Mechanistic Interrogation of BET Bromodomain Degraders for the Treatment of Metastatic Castration-Resistant Prostate Cancer

BIPOLAR ANDROGEN THERAPY: BREAKING OUT OF THE CHRYSALIS OF CHRONIC ANDROGEN DEPRIVATION THERAPY IN MEN WITH LATE-STAGE CASTRATE-RESISTANT PROSTATE CANCER

Samuel Denmeade, Ph.D., Johns Hopkins University

Treatments to block or lower testosterone have been the standard therapy for prostate cancer since the seminal work of Charles Huggins on suppression of androgens in the 1940s. Men with prostate cancer are typically treated with androgen ablation therapy; however, those treatments often stop working and result in the development of CRPC. One way that this resistance may occur in these cells is adapting to a low testosterone environment while maintaining high levels of the androgen receptor. Paradoxically, studies have shown that CRPC cells can be growth-inhibited by treatment with extremely high levels of androgens. This novel and intriguing concept of using high-dose testosterone as a therapy for prostate cancer seemed counterintuitive and was initially met with much skepticism. Dr. Samuel Denmeade and colleagues at Johns Hopkins University (JHU) wanted to see whether this different approach to therapy would work and started by performing a small pilot clinical trial in which they learned that men with mCRPC could tolerate FDA-approved doses of testosterone that produced high blood levels of testosterone without worsening side effects or causing disease progression. With this, the concept of bipolar androgen therapy (BAT) was established, which consists of a treatment strategy where CRPC cells rapidly cycle between supra-physiological androgen levels and androgen ablation therapy.

With support from an FY13 PCRP Transformative Impact Award, Dr. Denmeade and his team performed a clinical study to expand on their previous clinical results, demonstrate that high-dose testosterone can be safely administered, and produce a therapeutic effect in men with CRPC, increase their quality of life, and potentially resensitize them to androgen therapy. With this



funding, they completed a randomized phase 2 study comparing BAT with the androgen inhibitor enzalutamide in asymptomatic men with CRPC (NCT02286921). For this TRANSFORMER (Testosterone Revival Abolishes Negative Symptoms, Fosters Objective Response and Modulates Enzalutamide Resistance) trial, they recruited 200 men from 17 research sites around the country. Surprisingly, even though these two therapies are the exact opposite of each other, they observed remarkably similar effects in these men and demonstrated the same time to disease progression (5.7 months), indicating that BAT did not enhance disease progression. Interestingly, they found that, while 25% of patients who received enzalutamide before BAT had an effective response to the treatment, the response rate for patients who received enzalutamide after BAT was 75%, and the duration of their response was three times longer, meaning that it took longer for their prostate cancer to stop responding to treatment. Finally, they showed BAT can enhance quality of life and restore sexual function in some men.

These results suggest that, in addition to a primary response from BAT treatment, high-dose testosterone has the potential to increase the duration of response to androgen ablative therapies like enzalutamide and may enhance quality of life after treatment. Based on these findings, the JHU team received an FY19 PCRP Clinical Trial Award to evaluate the effectiveness of repeat cycling between BAT and enzalutamide to determine whether this approach could extend the effectiveness of the therapy regimen while minimizing the side effects. The clinical trial opened in 2020 and is currently recruiting patients. The work of Dr. Denmeade and his team epitomizes the goal of the PCRP to support innovative research ideas that have the potential to make a significant impact on the lives of men living with prostate cancer – in this case, not only giving patients a prolonged or potentially an indefinite response to therapy, but also improving their quality of life. The true impact of this work on patient care will continue to emerge as more studies are performed. However, the results from the TRANSFORMER study suggest we may need to modify the current hormone therapy paradigm to incorporate periods of high-dose testosterone alternating with periods of androgen deprivation as a way to prolong the duration and magnitude of hormone response.

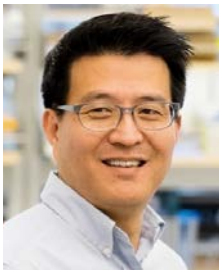
Additional Information:

Bipolar Androgen Therapy: Breaking Out of the Chrysalis of Chronic Androgen Deprivation Therapy in Men with Late-Stage Castrate-Resistant Prostate Cancer

Mr. Tom Hulsey

Prostate Cancer Survivor and Research Advocate, Consumer Peer Reviewer, ZERO – The End of Prostate Cancer

"It is such an honor to part of this impactful program. The scientific researchers need to hear from survivors: the human experience of prostate cancer and the impact it is having on families. As funding continues, the DOD PCRP is moving toward a cure and eradication of prostate cancer, but it is our responsibility as survivors to keep the research momentum going. I've learned from participating on six different panels that the scientists really do listen and respect my perspective ("lived experience"), which sometimes challenges and influences their review. And importantly, my vote counted every bit as much as each of the scientist reviewers."



REVOLUTIONIZING PROSTATE CANCER IMAGING WITH COLLAGEN HYBRIDIZING PEPTIDE

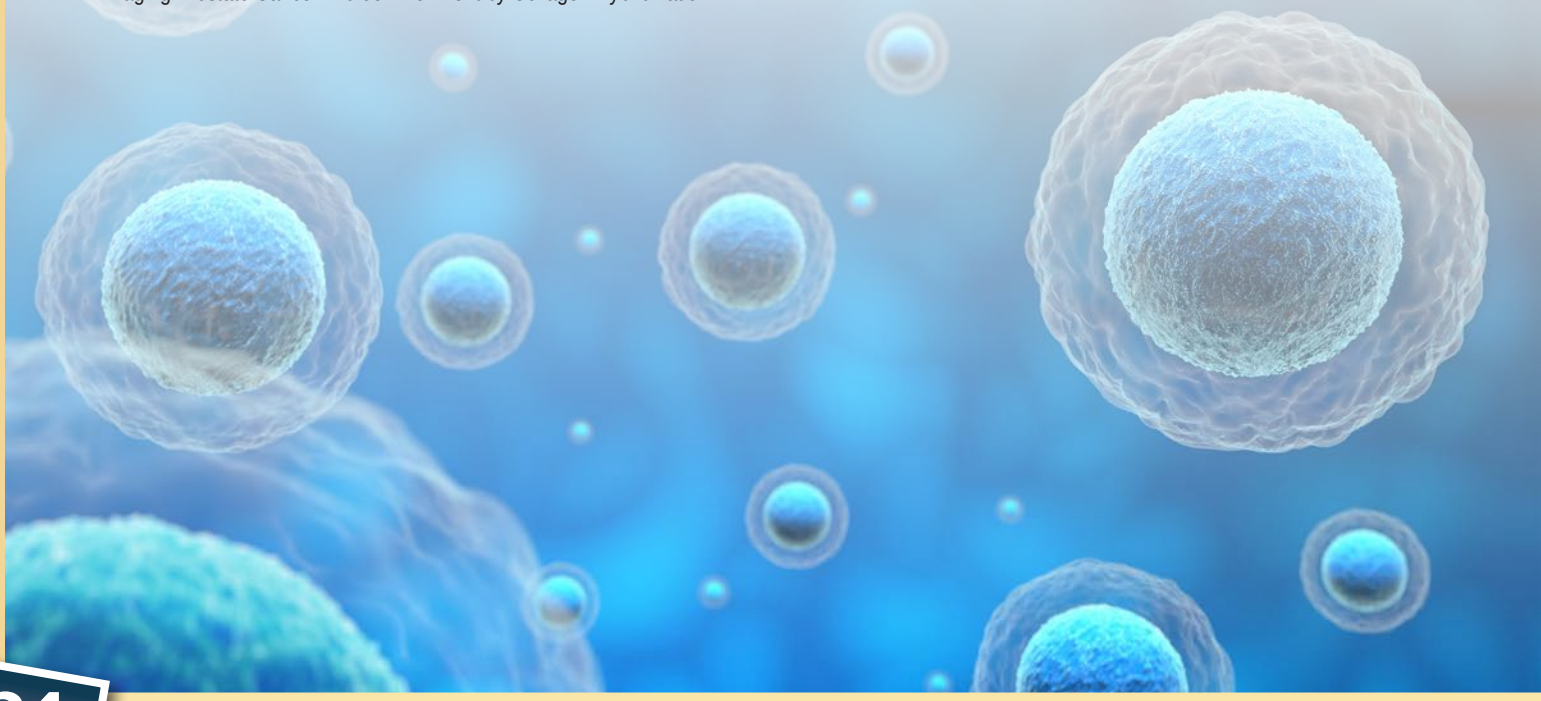
Michael Yu, Ph.D., University of Utah
Martin Pomper, M.D., Ph.D., Johns Hopkins University

One of the most pressing issues in prostate cancer management is the need to predict, at the time of diagnosis, which tumors will remain indolent and which will progress rapidly, ultimately helping patients avoid unnecessary treatment of clinically insignificant disease. Dr. Michael Yu at the University of Utah and Dr. Martin Pomper at Johns Hopkins University have discovered a novel way of identifying aggressive prostate cancer by looking at the environment surrounding the tumor cell instead of the tumor cell itself.

While working with collagen hybridizing peptide for tissue engineering, Drs. Yu and Pomper serendipitously discovered that this peptide has an affinity to denatured, or damaged collagen, which has been shown to exist in the microenvironment of cancer cells that have begun to invade and metastasize. Collagen serves as the basic scaffold for cells in most human tissues, including normal prostate tissues, and has been shown to become structurally damaged as cancer cells develop and begin to invade surrounding tissues. Drs. Yu and Pomper realized that, with a peptide that has a strong affinity for damaged collagens, they could develop a novel method for detecting damaged collagens that could be used not only for detecting aggressive tumors, but also for drug delivery. With support from an FY11 PCRP Synergistic Idea Development Award, Drs. Yu and Pomper began working to develop and test a simple molecular probe, now known as collagen hybridizing peptide (CHP) (Bennink LL 2017), for the purpose of detecting aggressive prostate cancer.

After successfully being able to image invasive cancer in an animal model using fluorescent CHP, they have been working to translate these results to humans, which requires application of imaging modalities that are conducive to human use, such as radioactive metals (for positron emission tomography [PET]) and MRI active molecules and nanoparticles. Their initial attempts at producing radioactive CHP encountered challenges with peptide stability and the ability to make multimeric structures out of CHP (by conjugating to polymers or PEG scaffold), but the team has been working on some new strategies for turning CHP into PET and MRI imaging agents and is confident that they will be able to find the right strategy for developing these compounds. Collagen hybridizing peptide has been commercialized for research use (sold by 3Helix Inc), which will better enable further research efforts by this team and others and may enable to expansion of using collagen peptides for detecting other conditions that are associated with collagen breakdown, including arthritis, fibrosis, and osteoporosis. Drs. Yu and Pomper hope that their research will help the many men who will be faced with an uncertain diagnosis of prostate cancer to better enable them to make the appropriate treatment decisions depending on the aggressiveness of their disease.

Additional Information:
Imaging Prostate Cancer Microenvironment by Collagen Hybridization



IN THE CLINICAL PIPELINE

The PCRP has invested in the discovery and development of multiple therapies and diagnostic tools since the beginning of the program, many of which have continued to advance through the clinical pipeline. The current research phase of agents that have been supported by the PCRP at some point in their clinical development are condensed below, with more information shown on pages 26-31.

	Preclinical	Phase 1/2	Phase 2/3	To Patients
Biomarkers		1 Agent or Technique		3 Agents or Techniques
Imaging	2 Agents or Techniques	4 Agents or Techniques	1 Agent or Technique	4 Agents or Techniques
Mechanisms of Resistance and Response	1 Agent or Technique	1 Agent or Technique		
Targeted Therapy	3 Agents or Techniques	6 Agents or Techniques	1 Agent or Technique	3 Agents or Techniques
Combination Therapy	1 Agent or Technique			
Hormonal Therapy		4 Agents or Techniques		3 Agents or Techniques
Immunotherapy		7 Agents or Techniques	1 Agent or Technique	
Radiotherapy	1 Agent or Technique	1 Agent or Technique	1 Agent or Technique	
Chemotherapy		3 Agents or Techniques		1 Agent or Technique

PCRP Clinical Pipeline Successes

	Agent/Technique	Principal Investigator(s), Award Mechanism, Description
BIOMARKERS		
Phase 1/2	CDK12	***Marcin Cieslik;*** *Idea Development Award – New Investigator Option* The phase 2 CheckMate 650 trial is expanding to gain insight into the predictive value of biomarkers as well as adjusting drug dosing and frequency to reduce side effects of checkpoint inhibitor immunotherapy with nivolumab and ipilimumab combination therapy followed by nivolumab monotherapy in patients with mCRPC with CDK12 mutations.
To Patients	AR-V7 mRNA assay	***Jun Luo, Stephen Plymate, Johann de Bono;*** *Biomarker Development Award* A clinically validated non-invasive assay to detect AR-V7 mRNA in circulating tumor cells in the blood using Adna Test technology, which led to an improved RNA in situ hybridization assay capable of visualizing and quantifying AR-V7 mRNA in CRPC patients. This assay is commercially available as the AdnaTest ProstateCancer (Qiagen) for research use to detect AR-V7 in blood and investigate resistance to potential mCRPC drugs.
	Oncotype DX AR-V7 Nucleus Detect Test	***Howard Scher;*** *Transformative Impact Award* A liquid biopsy assay that measures AR-V7 levels in the nucleus of tumor cells circulating in the blood and can help predict whether a patient's prostate cancer will be responsive to taxane-based chemotherapy or androgen receptor signaling inhibitors. This liquid biopsy assay is commercially available as the Oncotype DX AR-V7 Nucleus Detect Test (Genomic Health/Epic Sciences) to better guide treatment decision-making.
	NuSAP1 Marker (Prolaris, Decipher assays)	***James Brooks;*** *Idea Development Award – Established Investigator* The PCRP funded early work characterizing NuSAP1 overexpression in recurrent prostate cancer tumors and validated its potential as a prognostic marker. NUSAP1 is part of the Prolaris® and Decipher® gene expression tools that have been validated in several clinical contexts as prognostic in early-stage prostate cancer in human patients.
IMAGING		
Preclinical	T2-weighted prostate MRI at 7 Tesla (T) using a simplified external transmit receive coil array	***Andrew Rosenkrantz;*** *Exploration Hypothesis Development Award* The 7T MRI scanner at New York University produces a magnetic field more than twice the strength of scanners currently found in the clinic. The team designed new hardware and software to take advantage of this ultra-high field scanner, which they tested on two prostate cancer patients, resulting in substantially improved image quality. An open-label interventional trial is now being conducted in 400 healthy participants to determine whether the technology can produce meaningful structural and physiological information.
	Electrical Impedance Spectroscopy for noninvasive detection of prostate tumors	***Ryan Halter;*** *Prostate Cancer Training Award, New Investigator Award, Idea Development Award and Synergistic Idea Development Award* This work developed a device to measure the electrical properties of prostate tissue using a technique called electrical impedance spectroscopy (EIS). After testing the properties of 64 prostate tissue samples (ex vivo), the investigator concluded that this device can distinguish between benign and cancerous tissue with high accuracy. The device was integrated into a standard prostate biopsy needle, and the investigator found very high correlation between EIS results and histopathology, which is the gold standard for diagnosis. Work is ongoing to combine this technology with trans-rectal ultrasound to allow less invasive diagnosis of prostate cancer.
Phase 1/2	124I-anti-PSCA A11 minibody	***Robert Reiter;*** *Laboratory Clinical Transition Award* A radiolabeled prostate stem cell antigen (PSCA) antibody fragment (minibody) was developed for PET imaging and demonstrated that it possesses excellent immunoreactivity and imaging contrast in animal models of prostate cancer. The PSCA minibody has the potential to advance prostate cancer imaging in the age of targeted therapies and to link the diagnosis and treatment of this disease more closely.
	MRI-guided robotic device for real-time needle placement in prostate biopsy sample retrieval	***Gregory Fischer;*** *Prostate Cancer Training Award, New Investigator Award* This MRI-guided robotic device is designed to guide a biopsy needle and brachytherapy seed placement while the patient is inside the MRI machine. This method provides greater precision than the currently used "blind" grid pattern method and is currently being tested in pilot clinical trials.

	Agent/Technique	Principal Investigator(s), Award Mechanism, Description
Phase 1/2	Fluorine-18 Fluorocholine PET	***Sandi Kwee;*** *New Investigator Award* Used to detect cancer by measuring the tissue metabolism of Fluorine-18 Fluorocholine (FHC), a substrate that is preferentially metabolized by cancer cells. This technique, combined with computed tomography (CT) scanning, can be used for whole-body detection of prostate cancer and to improve guidance of radiation therapy. Phase 1/2 clinical trials showed that 18F FC PET/CT can be used for localizing resistant tumors, which could potentially complement other measures of response in the precision management of advanced prostate cancer.
	RSI-MRI	***David Karow;*** *Idea Development Award - New Investigator* A non-invasive MRI technique for detecting and distinguishing aggressive from indolent prostate cancer by measuring the restricted diffusion of water within a cell, which differs between normal prostate tissue and cancerous tissue due to alterations in cell morphology. Restriction spectrum imaging (RSI) is being expanded through a whole-body cancer detection protocol for early metastatic disease and response to radiotherapy. RSI is now the standard of care at the University of Califonia, San Diego.
Phase 2/3	68 Ga DOTA Bombesin (68Ga-RM2)	***Andrei Iagaru;*** *Impact Award - Clinical Trial* 68Ga-RM2 PET will be used in combination with conventional MRI as a targeted approach for improving the detection of biochemical recurrence (i.e., rising PSA) and negative conventional imaging, with a focus on early detection of sites of disease that can be treated. Early results indicate that 68Ga-RM2 PET imaging can enhance the detection of recurrent cancer lesions in the body compared to conventional MRI.
To Patients	PMSA-based PET Imaging Agent	***Martin Pomper;*** *Idea Development Award* A PET radiotracer, 18F-DCFBC, was developed that targets the prostate-specific membrane antigen (PSMA), which is associated with higher Gleason grade, more aggressive disease. This early work led to the development of additional PSMA-PET imaging agents, two of which are now FDA-approved: Pylarify (18F-DCFPyL) and 68Ga PSMA-11.
	MRI-Based Treatment Planning for Radiotherapy	***Lili Chen;*** *New Investigator Award, Idea Development Award* An MRI-based treatment planning protocol for inverse planning technique for prostate intensity modulated radiation therapy (IMRT) was developed that specifically targets prostate tumor tissue and avoids damaging normal tissues and organs. This protocol has several advantages over CT imaging, including reduction in patient and staff time, savings in treatment costs, and decreased patient radiation exposure from CT scans. It has become a standard technique for IMRT of prostate cancer at the Fox Chase Cancer Center.
	Quantitative Total Bone Imaging Software (QTBI)	***Glen Liu;*** *PCCTC* Quantitative Total Bone Imaging Software (QTBI) automatically identifies and contours tracer update in bone for full or partial body imaging scans by fusing a series of scans from a patient over time, enabling evaluation of changes to each tumor hotspot and determination of treatment response by individual tumor metastases.
	Elekta Synergy	***David Jaffray;*** *Phase 2 New Investigator Award* A cone-beam CT imaging system capable of pinpointing the exact position of the prostate and support structures to deliver high doses of radiation to the tumor while minimizing damage to adjacent normal tissues. Today, this approach is used as the standard for precision radiation treatment of prostate and other cancers; over 80% of radiation machines sold today are equipped with it.
MECHANISMS OF RESISTANCE AND RESPONSE		
Preclinical	N-Cadherin monoclonal antibodies	***Zev Wainberg, Rob Reiter, Matthew Rettig;*** *Physician Research Training Award, Synergistic Idea Development Award* N-Cadherin was identified as responsible for metastasis and castration resistance, and these effects were inhibited in vivo with N-cadherin-specific antibodies, suggesting this is a promising new target for prostate cancer treatment.
Phase 1/2	3βHSD1 mutation	***Zhenfei Li, Nima Sharifi;*** *Physician Research Training Award* Discovered a mechanism of resistance to ADT involving a gain-of-function variant allele (present in ~30% of men) in 3βHSD, a steroidogenic enzyme that promotes androgen production, prostate cancer growth, and development of CRPC. Recent results support the use of the 3βHSD variant allele as a predictive biomarker of resistance to androgen deprivation therapy (ADT) and response to non-steroidal CYP17A1 inhibitors. A phase 2 clinical trial studying 3βHSD genotype and the non-steroidal CYP17A1 inhibitor apalutamide is in progress.

	Agent/Technique	Principal Investigator(s), Award Mechanism, Description
	TARGETED THERAPY	
Preclinical	ACK1 Inhibitor	***Nupam Mahajan, Kiran Mahajan;*** *Exploration Hypothesis Development Award* Early PCRP-funded work identified ACK1 as a regulator of the AR pathway and showed that inhibition of ACK1 suppressed CRPC tumor growth and gene fusion expression in vivo. Preclinical pharmacokinetic, metabolic, and toxicological studies are now underway on a novel ACK1 inhibitor, (R)-9bMS, and its derivatives. The discovery of (R)-9bMS has been patented and licensed for development as a cancer drug.
Preclinical	J591- duocarmycin conjugate	***Neil Bander;*** *Laboratory Clinical Transition Award* This therapeutic was developed by linking J591, an antibody to PMSA, to duocarmycin, a DNA alkylating agent 1,000-fold more potent than doxorubicin. By using an antibody that is specific to only prostate cancer cells, the chemotherapy is delivered directly to tumor cells, thus minimizing side effects. This conjugate has been shown to be very effective in animal models.
Preclinical	KBU2046	***Raymond Bergan;*** *Laboratory–Clinical Transition Award* A derivative of genistein (a chemical in soy) was developed to specifically target prostate cancer cell motility. KBU2046 has been shown to inhibit metastasis and prolong survival in preclinical models of prostate cancer and is currently in current Good Manufacturing Practices production. The PCRP-supported preclinical studies required for Investigational New Drug (IND) application submission are underway.
Phase 1/2	Bcl-2 inhibitor venetoclax (ABT-199)	***Dean Tang;*** *Idea Development Award* ABT-199, a BCL-2 inhibitor, was identified in a drug screen for compounds that are effective in targeting AR-PSA- LNCaP prostate cancer stem cells. Additional preclinical experiments demonstrating that ABT-199 (venetoclax) in combination with enzalutamide prevents emergence of enzalutamide-resistant tumors over the course of treatment in mouse xenograft models have provided the foundation for an ongoing phase 1b/2 clinical trial testing this combination therapy.
Phase 1/2	Indomethacin plus Enzalutamide	***Chong-xian Pan, Allen Gao, Christopher Evans;*** *Impact Award – Clinical Trial – Partnering PI Option* A Phase 1/2 clinical trial is ongoing to test the combination of indomethacin and enzalutamide for efficacy in patients with progressive CRPC following abiraterone treatment. The steroidogenic enzyme Aldo-Keto Reductase Family 1 Member C3 (AKR1C3), is overexpressed in prostate cancer and is associated with the development of resistance to enzalutamide and abiraterone treatment. Indomethacin inhibits AKR1C3 activation and can resensitize resistant CRPC cells to enzalutamide and abiraterone.
Phase 1/2	C-209	***Hatem Sabaawy;*** *Synergistic Idea Development Award* A BMI-1-inhibitor that inhibits prostate cancer growth and metastasis and can boost the effectiveness of chemotherapy. Pharmacological improvement of C-209 is now underway, and several C-209 derivatives have been tested in phase 1b clinical trials of childhood glioma and ovarian cancer.
Phase 1/2	BET Inhibitor (ZEN003694)	***James Korkola and Joshi Alumkal;*** *Synergistic Idea Development Award* BET bromodomain inhibitor, ZEN003694, was shown to suppress androgen or enzalutamide activation of mutant F877L AR and block enzalutamide-induced growth of mutant F877L AR CRPC tumors in mice. ZEN-003694 was tested in a phase 1 clinical trial sponsored by Zenith Epigenetics. A phase 1/2 trial testing the combination of ZEN-003694 and enzalutamide in patients with mCRPC is currently recruiting.
Phase 1/2	Mipsagargin	***Sam Denmeade;*** *Idea Development Award* Developed by coupling a PMSA-specific peptide to the analog of the plant-derived toxin Thapsigargin. This prodrug is inactive until it encounters PSMA on the surface of prostate cancer cells, at which point it is activated and selectively kills tumor cells with minimal side effects. A phase 2 clinical trial of G-202 in patients with localized, high-risk prostate cancer prior to prostatectomy has been completed.
Phase 1/2	Durvalumab plus Olaparib	***Fatima Karzai;*** *Physician Research Award* Preliminary results of a pilot clinical study suggest that a combination of the poly (ADP-ribose) polymerase (PARP) inhibitor, olaparib, and the anti-PDL-1 antibody, durvalumab, in men with mCRPC dramatically reduce PSA levels and measureable metastatic lesions, regardless of mutational status. A phase 2 clinical trial of olaparib and durvalumab is currently underway in an expansion cohort of men with mCRPC following enzalutamide or abiraterone treatment.

	Agent/Technique	Principal Investigator(s), Award Mechanism, Description
Phase 2/3	Niraparib	***PCCTC Involvement*** Niraparib is a PARP-inhibitor that received FDA breakthrough designation in 2019 for BRCA1/2 gene-mutated mCRPC patients who have received prior taxane chemotherapy and AR-targeted therapy.
To Patients	Rubraca	***Wassim Abida;*** *PCCTC Involvement* Rubraca is a PARP-inhibitor approved for treatment of CRPC that has metastasized or has specific inherited (germline) mutations, such as BRCA1/2.
	Velcade® (PS-341)	***David McConkey;*** *New Investigator Award* The PCRP supported preclinical studies on PS-341, a proteasome inhibitor. Despite failing as a drug candidate for prostate cancer, Velcade® is approved for the treatment of multiple myeloma and relapsed mantle cell lymphoma.
	Xgeva® (Denosumab)	***Evan Keller;*** *Idea Development Award* An FDA-approved antibody that slows the progression of prostate cancer bone metastases, Xgeva® blocks the bone resorption protein, RANKL, thus slowing bone loss during cancer treatment. Xgeva® is the number one prescribed agent by oncologists in the U.S. for the prevention of skeletal-related events in patients with bone metastases. The drug indication has been expanded to include multiple myeloma patients.
COMBINATION THERAPY		
Preclinical	Veliparib (ABT888) plus radiation	***Phyllis Wachsberger;*** *Exploration Hypothesis Development Award* A new class of anti-cancer compound (PARP inhibitors), Veliparib (ABT888) plus radiation was shown in animal models to sensitize prostate cancer tumors to radiation, thus making the radiation more effective at reducing tumor growth.
HORMONAL THERAPY		
Phase 1/2	ARV-110	***Craig Crews;*** *Idea Development Award* Phase 1 dose escalation study assessing the safety and tolerability of ARV-110, a PROAC degrader, in men with mCRPC who have progressed on at least two prior approved systemic therapies for their castration-resistant disease (one of which must be enzalutamide or abiraterone).
	Mifepristone plus Enzalutamide	***Russell Szmulewitz;*** *Clinical Exploration Award* Glucocorticoid receptor (GR) signaling has been shown to compensate for androgen blocking by other hormonal therapies, thus leading to CRPC progression. The PCRP is funding phase 1 and 2 clinical trials to study the combination of Mifepristone, a GR blocker, in addition to enzalutamide, an AR blocker, to determine whether this combination treatment can overcome ADT resistance in patients with CRPC.
	3,3'-diindolylmethane (DIM)	***Stephen Safe;*** *Idea Development Award* A compound found in cruciferous vegetables (e.g., broccoli, cabbage), was shown to act as an anti-androgen, suppress AR-V7 expression, and slow the growth of prostate cancer cells. DIM has progressed to phase 1 and 2 clinical trials.
	N-terminal domain inhibitor (EPI-506)	***Marianne Sadar and Stephen Plymate;*** *Idea Development Award, Synergistic Idea Development Award* EPI-506 is the first and only small molecule inhibitor that binds to Tau5 of the androgen receptor N-terminal domain and can block transcriptional activities of truncated splice variants of androgen receptor. Unlike other hormonal therapies, this drug's mode of action may be able to overcome CRPC. ESSA Pharma, Inc., is developing next-generation N-terminal domain (NTD) inhibitors (Anitens), which are structurally similar to EPI-506, with improved pharmacological profiles and increased potency. The Aniten compounds are currently at the IND lead-selection stage, with an IND application filing expected to occur in early 2020.

	Agent/Technique	Principal Investigator(s), Award Mechanism, Description
To Patients	Erleada™ (Apalutamide)	***Howard Scher;*** *Clinical Consortium Award* The PCCTC led the early clinical development (phase 1/2 clinical trials) of apalutamide, resulting in a successful phase 3 clinical trial, known as SPARTAN. Erleada™, a next-generation androgen receptor signaling inhibitor, was the first anti-androgen therapy approved by the FDA for non-metastatic CRPC patients. Its FDA-approved indication was recently expanded to men with mCRPC.
	ZYTIGA® (Abiraterone acetate)	***Howard Scher;*** *Clinical Consortium Award* An anti-androgen was FDA-approved for the treatment of men with mCRPC through clinical testing by the PCRP-funded PCCTC. The FDA recently expanded the indication for Xtandi® to men with metastatic castration-senistive PCa.
	Xtandi® (Enzalutamide)	***Howard Scher;*** *Clinical Consortium Award* Inititally FDA-approved for the treatment of men with mCRPC. It works by blocking androgens, and has been shown to significantly delay cancer progression and prolong life. The FDA recently expanded the indication for Xtandi® to men with non-mCRPC and men with mCRPC.
IMMUNOTHERAPY		
Phase 1/2	PSA 146-154 peptide vaccine	***David Peace;*** *Idea Development Award, Phase 2 Idea Development Award* The PSA vaccine has been shown to be effective in patients with high-risk, locally advanced or metastatic hormone-sensitive prostate cancer. Men who developed specific T-cell immunity following vaccination demonstrated greater overall survival.
	BP-GMAX-CD1	***Kevin Slawin;*** *Idea Development Award* BP-GMAX-CD1 is a novel dendritic-cell vaccine engineered to combine an immune-activating agent, AP1903, and the ARGENT™ cell-signaling regulation technology. The technology behind BP-GMAX-CD1 allows for precise activation of a potent and durable immune response. Preliminary results of a phase 1/2 trial in patients with advanced, androgen-independent prostate cancer demonstrated anti-tumor activity with PSA declines and tumor regression.
	DNA vaccine encoding Prostatic Acid Phosphatase (pTVG-HP)	***Doug McNeel;*** *Clinical Trial Award, Laboratory Clinical Transition Award, Postdoctoral Traineeship Award* pTVG-HP has been shown to stimulate an immune response to prostatic acid phosphatase (PAP), a protein specific to prostate cancer cells. This vaccine is currently being tested in phase 1/2 clinical trials in combination with anti-PD1 antibody treatment in patients with both early- and late-stage prostate cancer.
	MEDI6383 (OX40 Antibody)	***Andrew Weinberg;*** *Laboratory Clinical Transition Award* MEDI6383 binds to a protein on white blood cells, called OX40, which is highly expressed in men with advanced prostate cancer. This antibody stimulates the immune system and has been shown to provide anti-tumor benefit. A phase 1b clinical trial in partnership with Medimmune has been completed.
	Lm-PCaVx (ADU-741)	***Dirk Brockstedt;*** *Laboratory Clinical Transition Award* Lm-PCaVx is a listeria-based vaccine designed to stimulate an immune response to three prostate cancer antigens. An open-label phase 1 clinical trial to test the safety and immunogenicity of JNJ-64041809 in patients with mCRPC was initiated in 2015.
	MDA-7/IL-24	***Paul Fisher and Xiang-Yang Wang;*** *Synergistic Idea Development Award* A novel T-cell-based platform that uses the cytokine melanoma differentiation-associated gene-7/Interleukin-24 (MDA-7/IL-24) in combination with adoptive T-cell therapy for improved treatment of metastatic prostate cancer. An MDA-7-luciferase fused protein has been developed for monitoring the trafficking of adoptively transferred T-cells and therapeutic response.
	Adenoviral PSA Vaccine	***David Lubaroff;*** *Clinical Trial Award* An adenoviral PSA vaccine has been tested in two phase 2 clinical trials in patients with recurrent prostate cancer or hormone-refractory prostate cancer. Preliminary results demonstrated that the vaccine is safe, produces anti-PSA T-cell responses, and reduces blood PSA levels in the majority of patients.

	Agent/Technique	Principal Investigator(s), Award Mechanism, Description
Phase 3	Ipilimumab	***Eugene Kwon;*** *Clinical Trial Award* Ipilimumab is a monoclonal antibody that activates the immune system is FDA-approved for the treatment of melanoma. In a PCRP-supported phase 2 clinical trial, it was shown to enhance response to ADT. A phase 3 clinical trial in men with metastatic prostate cancer who had not received chemotherapy was also completed. Ipilimumab is now being tested in combination with other therapies for multiple types of cancer.
RADIOTHERAPY		
Preclinical	Inverse planning technique for prostate IMRT	***Lei Xing;*** *Idea Development Award* An algorithm was developed using inverse planning to improve computer control of IMRT. The result was a faster, more robust treatment with a 10% increase in radiation dose and 60% reduction in treatment time.
Phase 1/2	177Lu-J591	***Scott Tagawa;*** *Clinical Trial Award* ***Neil Bander;*** *Laboratory Clinical Transition Award* An antibody drug conjugate was developed by linking an antibody to PMSA (J591), which is highly expressed in prostate cancer, to Lutetium-177(177Lu) to target radiation specifically to tumor cells, including those circulating in the blood. This targeted radiotherapy could prove curative for men with early-stage, undetectable, micrometastatic disease. 177Lu-J591 in combination with ketoconazole is currently being tested in patients with high-risk castrate biochemically relapsed prostate cancer in a phase 2 clinical trial funded by the PCRP.
Phase 3	Xofigo® (Radium-223)	***PCCTC Involvement*** Radium-223, which is FDA-approved for CRPC patients with symptomatic bone metastases and no known vexceral metastatic disease, is in a phase 3 study comparing the effects of using radium-223 along with docetaxel chemotherapy treatment versus using docetaxel alone.
CHEMOTHERAPY		
Phase 1/2	Gamitrinib	***Dario Altieri;*** *Laboratory Clinical Transition Award* Gamitrinib is a first-in-class mitochondrial-targeted small molecule Hsp90 inhibitor with potent anticancer activity and the ability to boost the effectiveness of other anticancer agents. An IND application was submitted to the FDA to allow clinical testing in patients. A PCRP-supported phase 1 clinical trial of Gamitrinib is now underway in patients with advanced and metastatic prostate cancer.
	Phenelzine sulfate	***Jean Shih;*** *Idea Development Award* Phenelzine sulfate is a monoamine oxidase A (MAOA) inhibitor slows prostate cancer tumor growth and metastasis to the bone. FDA-approved for the treatment of depression, phenelzine sulfate demonstrated efficacy in a phase 2 clinical trial for patients with biochemical recurrent castration-sensitive prostate cancer.
	Entinostat (MS-275)	***Roberto Pili;*** *New Investigator Award* Entinostat is a histone deacetylase inhibitor that was shown to halt the growth and proliferation of prostate cancer in vitro and in vivo. In a small phase 1 study, a combination of entinostat with 13-cis retinoic acid was shown to be reasonably well tolerated. Currently, there are ongoing phase 2 trials in Hodgkin's lymphoma, advanced breast cancer (in combination with aromatase inhibitors), and metastatic lung cancer (in combination with erlotinib).
To Patients	JEVTANA® (Cabazitaxel)	***PCCTC Involvement*** The PCCTC played a role in the development of cabazitaxel and now it is in phase 1/2 combination studies with enzalutamide and abiraterone for men with mCRPC. The FDA has approved cabazitaxel for use in combination with prednisone in patients with mCRPC who have been previously treated with docetaxel.

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03/2022
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