CDMRP

Department of Defense

Prostate Cancer Research Program

U.S. Army Medical Research and Materiel Command

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 $12 billion (B) in appropriations from its inception through fiscal year 2018 (FY18). Funds for the CDMRP are added to the Department of Defense (DoD) budget, in which support for individual programs such as the Prostate Cancer Research Program (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.

"It is impossible to overstate the impact this program has had on the lives of prostate cancer patients and their families. No other program works as hard to focus on science that has a meaningful and very rapid impact on lethal prostate cancer."

Bill Dahut, M.D., FY18 Programmatic Panel Chair, National Cancer Institute

Prostate Cancer Research Program

VISION

Conquer prostate cancer

MISSION

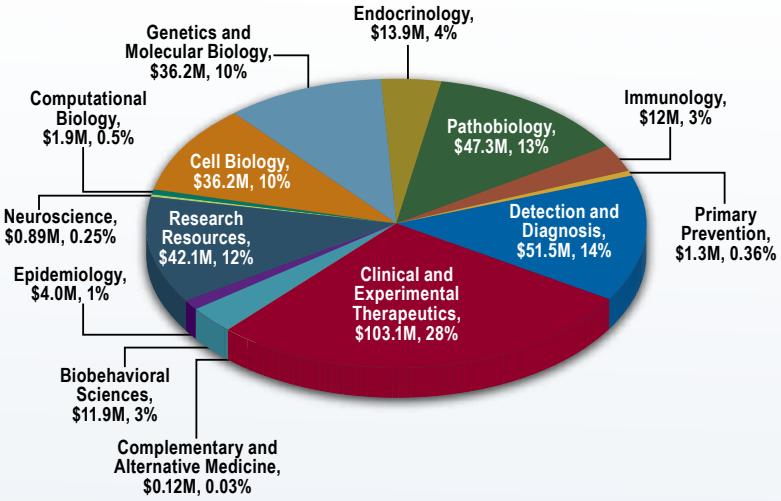
Fund research that will lead to the elimination of death from prostate cancer and enhance the well-being of Service members, Veterans, and all men experiencing the impact of the disease

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 $1.72B for the PCRP, including $100M in FY18. 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.

From FY13-FY17, the PCRP funded 548 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 prostate cancer patients, ultimately helping to realize the goal of making a direct, positive impact on patients and their families.

FY13–FY17 PCRP Research Portfolio



"As a Prostate Cancer Survivor and Support Group Leader, I cannot overemphasize how critical the Prostate Cancer Research Program is as a source of funding. It is so important that we continue our research to find a cure and more accurate screening methods to detect this dreaded disease."

Mr. Johnny Payne, Prostate Cancer Survivor and Research Advocate, National Alliance of State Prostate Cancer Coalitions Alliance

Moving the 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 overviews the prostate cancer research and funding environment and outlines the strategic direction of the PCRP in the hopes of providing greater clarity regarding the program's goals to the public and other stakeholders. The PCRP Strategic Plan will be reviewed during the program's annual Vision Setting meeting and updated as necessary.

OVERARCHING STRATEGIC GOALS

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 strategic goals that are critical to providing further advancements that will impact current and future prostate cancer patients. All PCRP applicants are required to address at least one of the following overarching strategic goals in order to facilitate progress toward these goals and priorities as part of the PCRP's Strategic Plan:

- ***Develop treatments that improve outcomes for men with lethal prostate cancer***
- ***Reduce lethal prostate cancer in African Americans, Veterans, and other high-risk populations***
- ***Define the biology of lethal prostate cancer to reduce death***
- ***Improve the quality of life for survivors of prostate cancer***

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

Field Toward Finding A Cure

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 advance the mission of the PCRP. The FY18 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 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 that 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

RESOURCES

Clinical Consortium Award*

Prostate Cancer Pathology Resource Network Award*

INNOVATION

Idea Development Award

NEW INVESTIGATORS

Early Investigator Research Award

Health Disparity Fellowship Award

Physician Research Award

New Investigator categories for Idea Development and Health Disparity Research Awards

IMPACT

Impact Award

Health Disparity Research Award

* While the Clinical Consortium Award and Prostate Cancer Pathology Resource Network Award are part of the PCRP's FY18 investment, these mechanisms were not offered for new awards in FY18.

The Prostate Cancer Biorepository Network (PCBN)

Accelerating the Clinical Translation of Biomarkers for Precision Medicine

The PCBN has established itself as the largest, most comprehensive prostate cancer biorepository in the world. Initiated in FY09, the PCBN is a PCRP-funded public resource that provides high-quality, well-annotated prostate cancer tissue (e.g., primary tumor, metastatic sites) and other patient samples (e.g., blood) to the prostate cancer research community. The PCRP envisioned a collaborative network of leading research institutions that would develop optimized processes and policies to collect and distribute prostate cancer biospecimens in a systematic, reproducible fashion, ultimately assuring researchers that PCBN-supplied samples are of the highest quality to address critical questions in prostate cancer research. Since its inception, the PCRP has contributed $9.34M to support the shared infrastructure and development of the PCBN, which currently includes five sites: Johns Hopkins University (the Coordinating Center); New York University; the University of Washington; Washington University in St. Louis; and the Institute of Cancer Research in London. These sites specialize in different types of patient samples and provide complementary resources, including metastatic tissue (rapid autopsy and lymph node); biospecimens with long-term follow-up for biochemical recurrence, metastasis, and death; active surveillance; hormone and neoadjuvant therapy; tissues from African American men; and patient-derived xenograft models.

Over the years, utilization of PCBN resources has dramatically increased, with distribution of more than 3,000 de-identified patient samples and tissue microarrays to 83 investigators around the world. Their efforts have resulted in 44 articles featured in highly respected journals such as *Nature, The New England Journal of Medicine, Proceedings of the National Academy of Sciences of the United States of America, Cancer Research,* and *The Journal of Clinical Investigation.* PCBN resources have been recently utilized to develop improved molecular diagnostic tools for detection of microsatellite instability, which is present in approximately 12% of prostate cancer patients; identification of androgen receptor (AR) variants associated with poorer patient response to anti-androgen therapy; and identification of new target antigens for immune-based therapy for distinct subtypes of advanced prostate cancer.[1, 2, 3] PCBN investigators have also contributed to biospecimen science, demonstrating the effects of ischemia and fixation time on biomarker signals; the impact of storage temperature on RNA from fixed tissue; and demonstrating that robotic prostatectomy does not adversely affect biospecimen quality. Today, the PCBN is the largest, most comprehensive prostate cancer biorepository in the world and is available to provide researchers the samples needed to accelerate prostate cancer research, particularly the translation of biomarkers for precision medicine (for additional information, see http://prostatebiorepository.org/).

References:

1. Hempelmann JA, Lockwood CM, Konnick EQ, et al. 2018. Microsatellite instability in prostate cancer by PCR or next-generation sequencing. *Journal for Immunotherapy of Cancer.* April; doi: 10.1186/s40425-018-0341-y.
2. Zhu Y, Sharp A, Anderson CM, et al. 2018. Novel junction-specific and quantifiable in situ detection of AR-V7 and its clinical correlates in metastatic castration-resistant prostate cancer. *European Urology.* May; doi: 10.1016/j.eururo.2017.08.009.
3. Lee JK, Bangayan NJ, Chai T, et al. 2018. Systemic surfaceome profiling identifies target antigens for immune-based therapy in subtypes of advanced prostate cancer. *Proc Natl Acad Sci U S A.* 115(19); E4473-E4482.

"As a consumer reviewer, reading research proposals and meeting scientists at the PCRP scientific review meetings gave me a greatly increased appreciation of how far we have advanced in our understanding and treatment of this complicated disease. I have worked with many prostate cancer patients and their families, and I try to help bring their point of view to the scientists. Equally importantly, I think, I now try to bring the point of view of the scientists back to the patients and families. I want people to understand that the difference between medical science and YouTube "cure your cancer" advice is enormous, and the battle against cancer requires public support for scientific research. The DoD PCRP is one of the pillars of this effort."

Mr. Alan Meyer, Prostate Cancer Survivor and Research Advocate, Malecare, Inc.

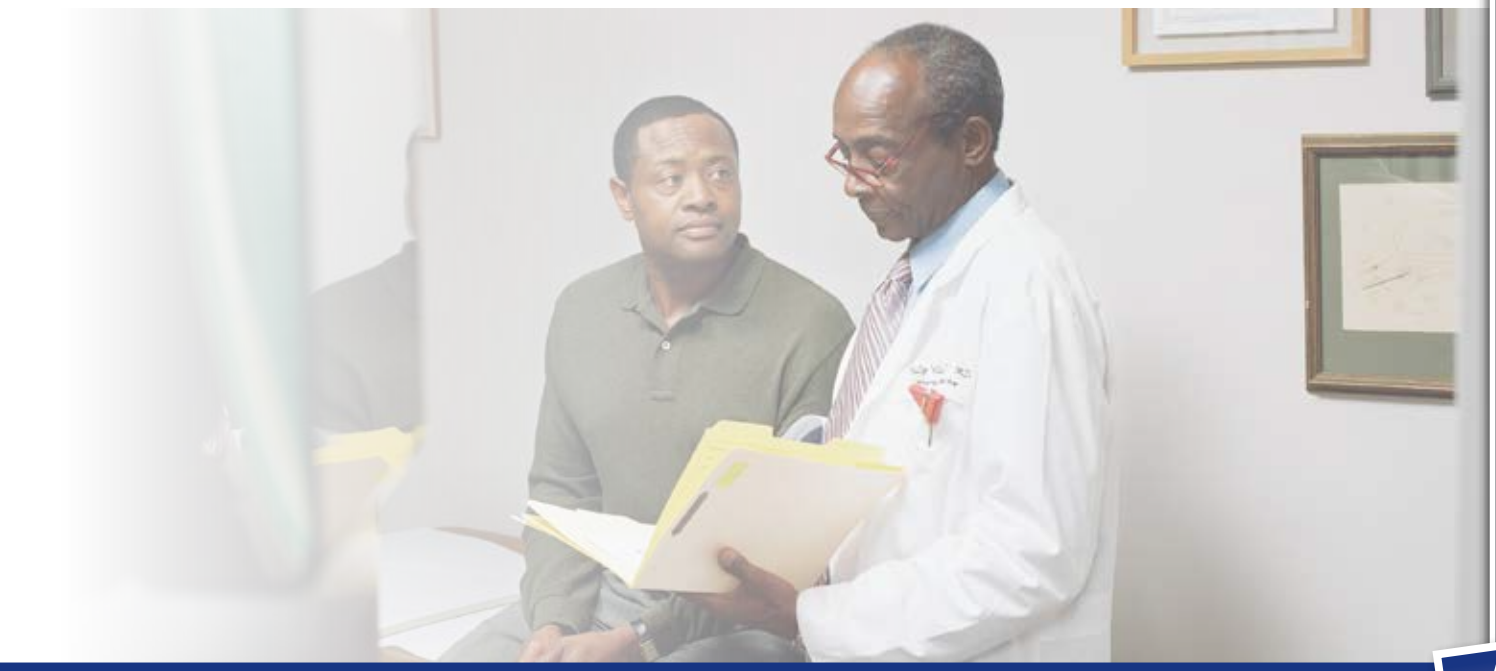
The North Carolina-Louisiana Prostate Cancer Project (PCaP)

Racial Differences in Financial Impact of Prostate Cancer Treatment and Outcome

Launched in FY02 with funding from a Consortium Overall Award, the PCaP represents the largest population-based study of newly diagnosed prostate cancer in African American and Caucasian American men ever conducted, with 2,258 participants. The study, under the leadership of Dr. James Mohler, collected a significant amount of personal and medical information, including income, health insurance coverage, treatments, and quality of life during and 5 years following prostate cancer diagnosis. Overall, the study found that racial differences in prostate cancer survival appear to originate more from a weak relationship of African American men with the American healthcare system, and poverty presents a significant obstacle to effective medical care for African American men compared to Caucasian American men. In addition, the PCaP developed and currently maintains a large repository of specimens (e.g., prostate cancer tissue, blood, and urine) collected from participants, which are also available for use by the prostate cancer research community. These specimens continue to inform studies that are investigating biological factors that contribute to prostate cancer health disparities. The results from recent follow-up studies utilizing PCaP data and specimens suggest that higher saturated fat or whole milk (versus lower-fat milk) intake is associated with an increased likelihood of developing more aggressive prostate cancer in both African American and Caucasian American men, whereas higher cholesterol intake is associated with more aggressive prostate cancer in only Caucasian American men.[1, 2] In FY16, the PCaP received additional PCRP funding through a Health Disparity Research Award (HDRA) to obtain 10-year follow-up data on the original group of prostate cancer patients and their caregivers. Although a variety of new Food and Drug Administration (FDA)-approved treatments (e.g., immunotherapy, anti-androgens, radiopharmaceuticals, and chemotherapies) are extending the lives of patients with metastatic castration-resistant prostate cancer (mCRPC), these treatments can also cause long-lasting side effects and be very expensive. Hence, many prostate cancer patients and their families will incur significant financial burden and stress as a result of a diagnosis of advanced prostate cancer. A critical goal of the FY16 HDRA project is to better understand the financial impact of prostate cancer treatment on patient survival and quality of life in both African American and Caucasian American men and to develop interventions to reduce the financial burdens and stress associated with a prostate cancer diagnosis (for further information, see https://pcap.bioinf.unc.edu/).

References:

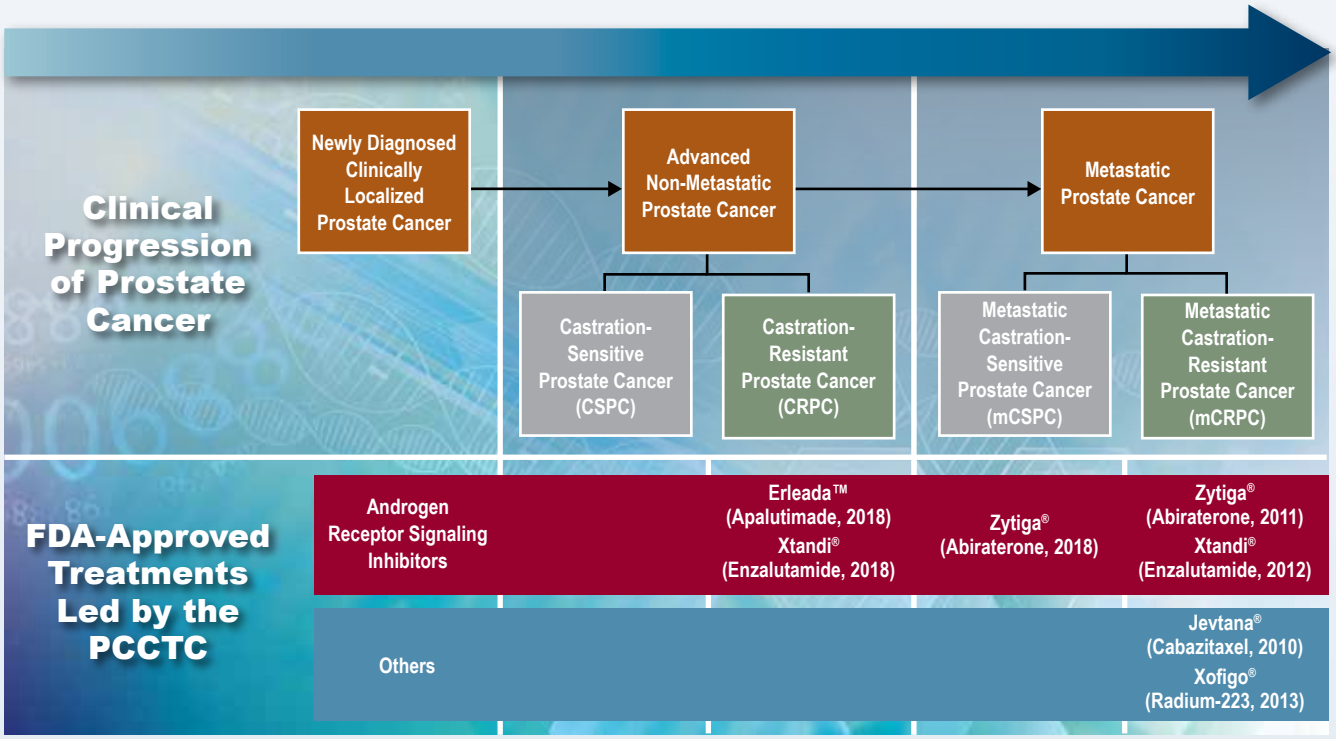
1. Steck SE, Omofuma OO, Su LJ, et al. 2018. Calcium, magnesium, and whole-milk intakes and high-aggressive prostate cancer in the North Carolina-Louisiana Prostate Cancer Project (PCaP). *Am J Clin Nutr.* 107(5):799-807.
2. Allott EH, Arab L, Su LJ, et al. 2017. Saturated fat intake and prostate cancer aggressiveness: results from the population-based North Carolina-Louisiana Prostate Cancer Project. Prostate Cancer Prostatic Dis. 20(1):48-54.



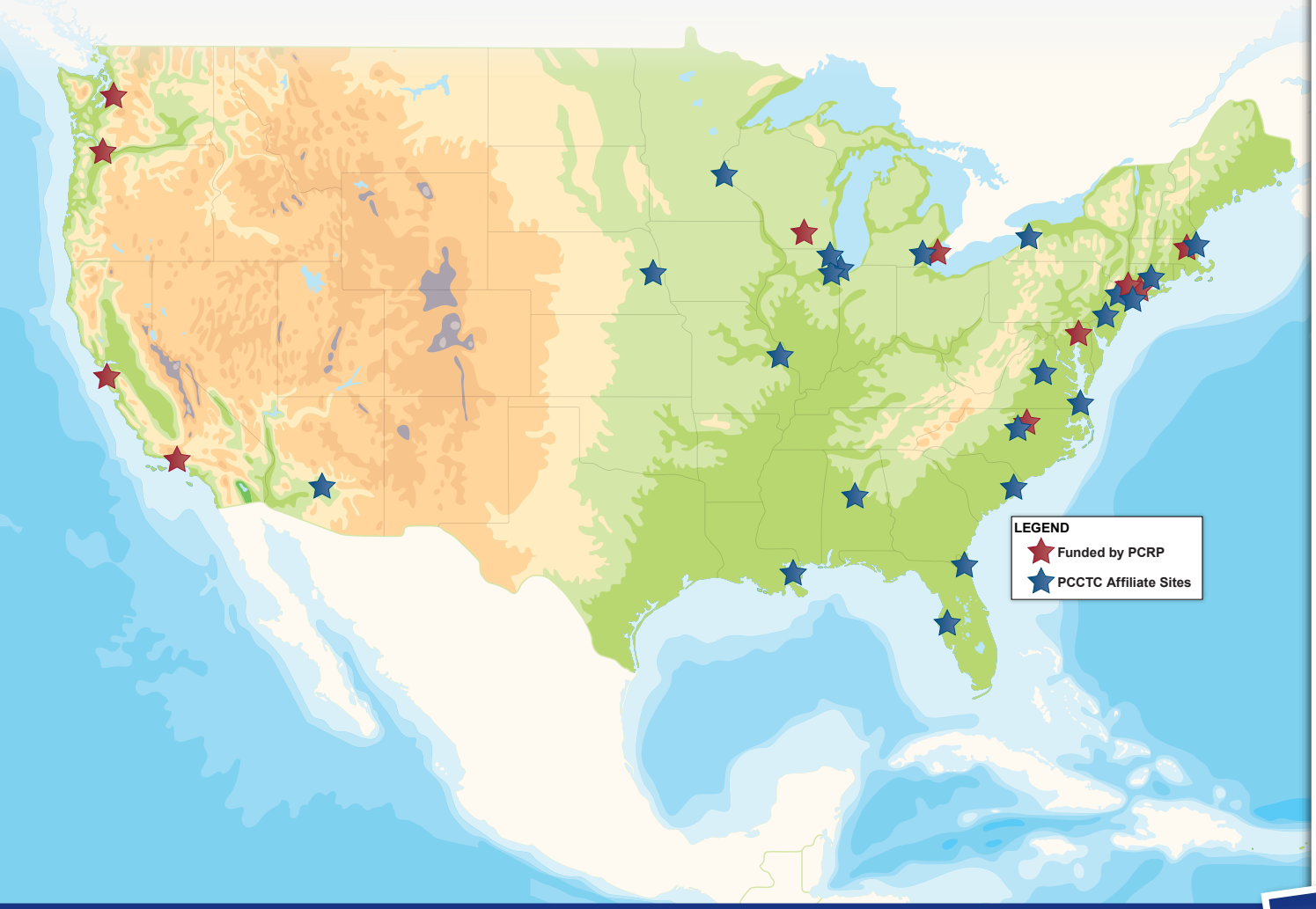
The Prostate Cancer Clinical Trials Consortium (PCCTC)

Transforming Prostate Cancer Treatment by Complementary Drug Development and Validation of Biomarkers Predictive of Successful Response

The PCCTC has established itself as the nation's premier prostate cancer clinical trials group and remains poised to make a significant impact on patients' lives by keeping the drug pipeline primed with promising novel agents. The PCCTC is a network of internationally recognized leaders in the prostate cancer field from the nation's top academic medical centers that employs a team-based approach to accelerate the development of promising drug candidates in early-phase (Phase I and I/II) clinical trials to Phase III clinical trials. PCCTC efforts impact clinical research through the complementary development of novel clinical trial designs, end points, and biomarkers that are predictive of successful response treatment. The PCCTC was established in 2005 through the collective efforts of the PCRP and the Prostate Cancer Foundation to provide a pipeline of high-impact, novel therapeutic interventions that would ultimately and significantly decrease the impact of prostate cancer on patients' lives. With the Memorial Sloan Kettering Cancer Center functioning as the coordinating center, the PCCTC now includes 10 PCRP-funded and 33 affiliated clinical research sites distributed across the United States and has incorporated as a limited liability company known as the Prostate Cancer Clinical Trials Consortium, LLC. Through PCRP funding in the amount of $59.2M, centralized management of research activities, rational selection of investigational agents, and collaborative trial design have resulted in the treatment of more than 7,400 prostate cancer patients in 214 clinical trials, which have produced over 100 published manuscripts and contributed to the advancement of 12 therapeutic candidates to Phase III study. Significantly, PCCTC-supported trials led to FDA approval of three novel drugs for patients with different



stages of advanced prostate cancer (see figure on page 8). Most recently, their research efforts have led to FDA approval of the first androgen inhibitors for men with non-mCRPC, which included the expansion of the indication for Xtandi® and the launch of Erleada® (Apalutimide). Equally important has been the PCCTC's work with regulatory authorities in developing biomarkers and surrogate end points that can be used for regulatory submissions to enable more rapid drug approvals, for example, the development of the Oncotype IQ AR-V7 Nucleus Detect Test, which can help predict patient response to certain therapies (see Howard Scher Highlight on page 16). In light of the evolving treatment landscape and advances in diagnostics, the PCCTC is also establishing an International Registry to Improve Outcomes in Men with Advanced Prostate Cancer, nicknamed "IRONMAN," with the goal of globally recruiting a racially and ethnically diverse group of 5,000 men with advanced prostate cancer to identify optimal treatment sequences and combinations and identify clinical and molecular subtypes of the disease to better understand variations in response to treatment. Through the collaborative nature and intellectual synergy of its leadership, the PCCTC remains poised to make a significant impact on patients' lives by keeping the drug pipeline primed with the most promising novel agents and validated biomarkers that are predictive of successful patient response (for additional information, see the interactive storyboard detailing the achievements of the PCCTC on the CDMRP website: http://cdmrp.army.mil/pcrp_timeline/timeline or the PCCTC website http://pcctc.org/).



Meta-Analysis of Phase III Trials Reveals Improved Survival for Black Men with Metastatic Castration-Resistant Prostate Cancer Treated with Docetaxel

Susan Halabi, Ph.D., Duke University

Black men are more likely than white men to both develop and succumb to prostate cancer, regardless of socioeconomic status. Only a few studies have assessed the differences in overall survival between black men and white men with mCRPC, and results to date have been conflicting regarding whether black men have less favorable survival outcomes than white men. Those studies were also notably confounded by the low recruitment of black men, which is not representative of the mCRPC patient population. With support from an FY14 PCRP Health Disparity Research Award, Dr. Halabi and her team are examining racial disparities associated with poor overall survival in men with mCRPC after receiving standard-of-care chemotherapy (docetaxel and prednisone [DP]).

Dr. Halabi's team performed a meta-analysis of nine Phase III clinical trials, totaling 8,820 mCRPC patients, of which only 6% were black men. The majority of patients recruited to the studies were white men (85%). The research team compared accrual rates across all nine clinical trials, noting that black mCRPC patients were enrolled at a higher rate in trials conducted by the National Cancer Institute's National Clinical Trials Network (12%) than those conducted by industry sponsors (4%).

Overall, black men enrolled in the nine trials were younger (with a median age of 67.6 years compared to 69.0 years for white men), but displayed higher baseline prostate-specific antigen (PSA) and testosterone levels than white men. The median overall survival duration was 21.0 (95% CI = 19.4-22.5) vs. 21.2 months (95% CI = 20.8-21.7) in black men and white men, respectively. The pooled multivariable hazard ratio was 0.81 (95% CI=0.72-0.91), which demonstrates that, overall, black men have a statistically significant decreased risk of death compared with white men (p-value<0.001). When the DP treatment groups from the trials were compared, black men fared slightly better than white men; black men had a median survival of 22 months, while white men had a median overall survival of 21 months.

Dr. Halabi recently presented the meta-analysis, which represents the largest comparative analysis of black and white men with mCRPC, at the 2018 American Society of Clinical Oncology Annual Meeting. She noted that, while these results are not generalizable to the U.S. population, they highlight the need to improve recruitment of minority populations into prostate cancer clinical trials to better understand racial variations in treatment response and survival. Dr. Halabi's current research is focused on identifying the genetic factors that underlie these observed differences in the treatment responses of black and white men, which may ultimately prove useful in predicting which black men with mCRPC will respond to docetaxel-based therapies and which should pursue other treatment strategies.

"In their commitment to conquer prostate cancer, the PCRP funds highly innovative and impactful basic, translational, and clinical research. It is a critical funding source for research that has risk, but also has a high potential to improve treatment paradigms for prostate cancer patients. Many of the advancements in the field of prostate cancer treatment over the last 20 years have stemmed from PCRP funding. While the PCRP has been unyielding in its mission to eliminate death from prostate cancer, they continuously evaluate the current needs of prostate cancer patients and modify their funding priorities accordingly. Two priorities that have remained steadfast at the PCRP is their involvement of patient advocates and their investment in the next generation of prostate cancer investigators. Their overall strategies have made the PCRP an invaluable funding resource for the development of prostate cancer cures"

Paula J. Hurley, Ph.D., Assistant Professor, The Brady Urological Institute and the Department of Urology, Johns Hopkins School of Medicine

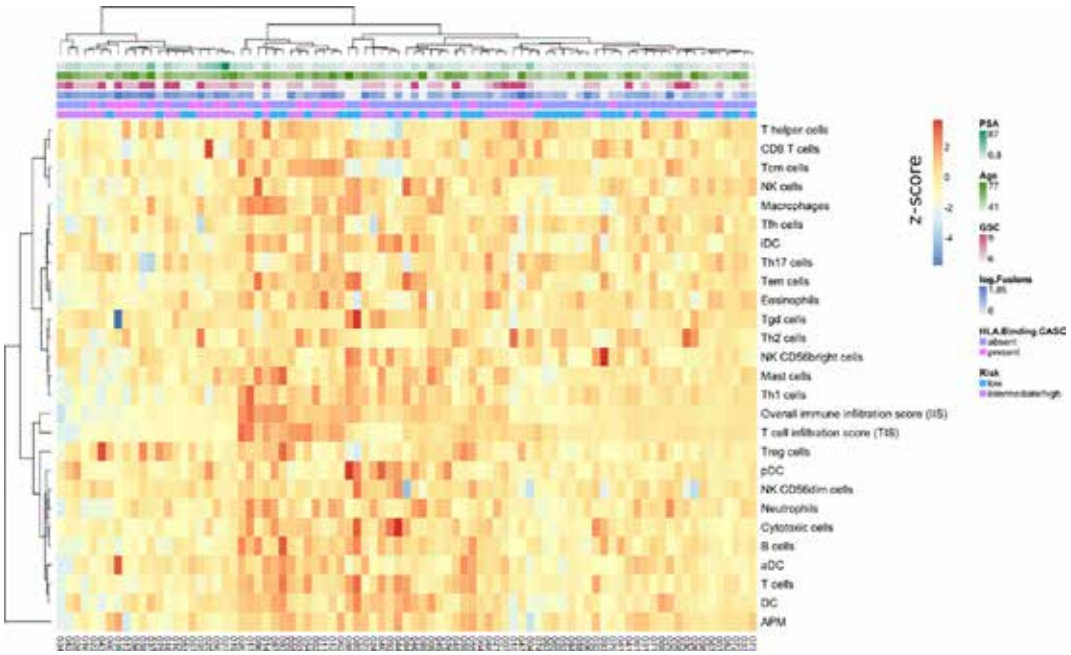
Chimeric Amino Acid Rearrangements as Immune Targets in Prostate Cancer

Julian J. Lum, Ph.D., BC Cancer

While cancer immunotherapy has shown remarkable success in some cancers, prostate cancer seems to be refractory. Dr. Julian Lum and his colleagues at BC Cancer wanted to find ways to overcome this barrier by identifying unique characteristics of prostate cancer that could be targeted by the immune system. It is known that prostate cancers contain types of mutation called gene-fusions, which are relatively rare in other epithelial cancers. These gene-fusions in turn give rise to unique features called chimeric amino acid sequences (CASQs). Dr. Lum and his colleagues hypothesized that CASQ sequences could serve as unique bar codes that the immune system can see and recognize as foreign.

With the support from an FY14 PCRP Exploration - Hypothesis Development Award , Dr. Lum and his multidisciplinary team of genomics and bioinformatics experts started by using highly sophisticated computational tools to identify all of the possible CASQs and decipher individual gene-fusions of human prostate cancer tumors. They found that all of the intermediate/high-risk patient tumors carried these mutations, whereas only 69% of the low-risk patient tumors were found to have gene-fusions. Upon further investigation, they were surprised to find that, as the cancer progressed, more mutations accumulated, and there were signs that the immune system was being shut off as a potential way for tumors to hide from detection by the immune system. These findings open up a potential new avenue to use gene-fusions as an immunotherapy target for prostate cancer.

In the next phase of their work, Dr. Lum is validating these results in a larger set of patients and applying a streamlined approach to quickly verify which gene-fusions can be targeted in order to activate the immune system. Dr. Lum notes, “We want to know why these mutations accumulate and seem to shut off the immune system. If this is true, we could potentially target these mutations using the immune system to turn the cancer on itself.” Ultimately, Dr. Lum intends that this work will lead to the development of personalized, tailor-made immunotherapies created based on a patient’s gene-fusion profile for the treatment of prostate cancer.



Low and intermediate-high risk prostate cancer patients have different immune profiles. Gene fusions and predicted CASQ-derived epitopes are associated with predictions of immune cell infiltration. This analysis depicts the predicted immune cell infiltrate levels and immunological parameters for both the low- and intermediate/high-risk cohorts. Colored annotation tracks represent patient characteristics, such as PSA level, age at diagnosis, Gleason score, log-predicted total tumor fusions, and predicted CASQ epitopes. In general, patients with strong expression of cytolytic immune genes harbored less tumor fusions and predicted CASQ epitopes, while patients with immune regulatory and Th2 expression signatures had more tumor fusions and predicted CASQ epitopes.

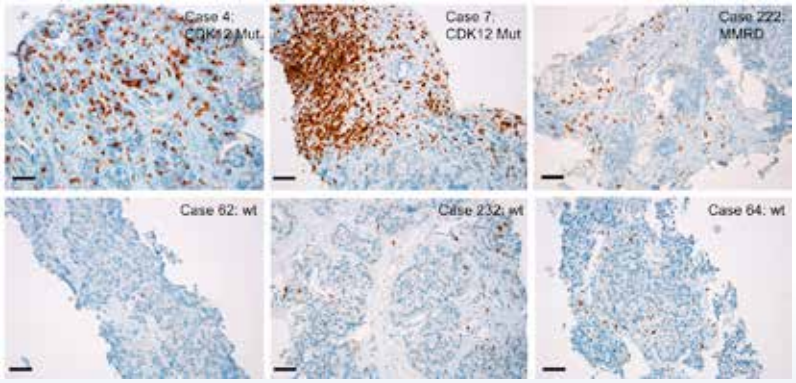
CDK12 Loss is a Distinct Immunogenic Class of Advanced Prostate Cancer

Marcin Cieslik, Ph.D., University of Michigan

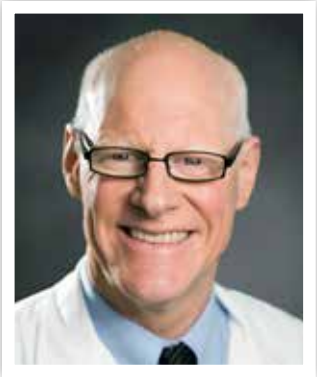
Prostate cancer is a heterogeneous disease, meaning that not all prostate cancer cells will progress at the same rate, and they may vary in their response to different therapies, which will ultimately affect a patient's overall survival. This heterogeneity stems from differences that exist at the molecular level, so researchers have been looking to identify prognostic biomarkers to guide treatment decisions. Dr. Marcin Cieslik and his colleagues at the University of Michigan hypothesized that cellular immune signatures, such as tumor infiltrating lymphocytes and immune checkpoints, can predict survival in mCRPC. Furthermore, this difference in survival could be due to a stronger and more diverse immune phenotype that could result in better outcomes to immunotherapy, which has been an elusive treatment strategy for prostate cancer patients in general.

Dr. Cieslik's team began by focusing their research on a specific subtype of prostate cancer cells that contain mutations in the CDK12 gene. CDK12 is a cyclin-dependent kinase that regulates several critical cellular processes, and previous work from this group has shown that CDK12 mutations are enriched in mCRPC. With support from an FY16 PCRP Idea Development Award, Dr. Cieslik examined the ability of immune cells to infiltrate and escape from CDK12-mutant mCRPC tumors, and the results confirmed that CDK12-mutant prostate cancer is a unique molecular subtype associated with extensive immune infiltration. Specifically, CDK12-mutant tumors showed an increased expression of immune signaling proteins, called chemokines, as well as their receptors, which presumably allowed for better infiltration of the immune cells into the mCRPC tumors. This data suggest that patients whose mCRPC contains CDK12 mutations may respond well to immunotherapy, justifying further investigation at the clinical level.

These results are now being translated to patients through an investigator-initiated Phase II clinical trial titled, "Immunotherapy in Patients with Metastatic Cancers and CDK12 Mutations (IMPACT)." This multi-center trial is being sponsored by the University of Michigan Cancer Center, with Dr. Ajjai Alva as the Principal Investigator, and will also be recruiting patients at the Memorial Sloan Kettering Cancer Center and the University of California, San Francisco. This Phase II study will evaluate the efficacy of checkpoint inhibitor immunotherapy (nivolumab and ipilimumab combination therapy, followed by nivolumab monotherapy) in mCRPC patients with CDK12 mutant tumors, and is now open for enrollment (see NCT03570619 on clinicaltrials.gov for more information). Further validation of Dr. Cieslik's hypothesis in the clinic would not only benefit the practice of precision medicine for men with mCRPC, but may also provide answers for how to better harness the power of immunotherapy for other disease subtypes.



Immunohistochemistry performed on formalin-fixed paraffin-embedded tumor sections using anti-CD3 antibody (immune marker). Six representative cases are shown, including two CDK12 mutant tumors, one mismatch repair deficient (MMRD) tumor, and three tumors that are wild-type for CDK12, mismatch repair genes, and homologous recombination genes. Black bar, 50 mm.



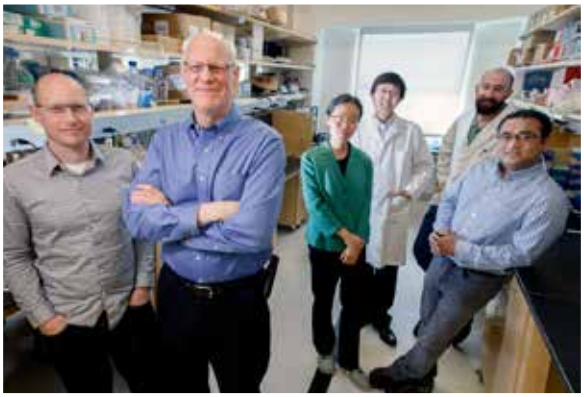
Inhibiting Prostate Cancer Cell Motility to Prevent Lethal Prostate Cancer

Raymond Bergan, M.D., Oregon Health & Science University

The majority of deaths due to prostate cancer occur as a result of the spread of cancer cells from the original tumor to distant sites in the body, a process known as metastasis, which results in the destruction of the tissues and organs to which the cancer has spread. Metastasis is a multi-step process that includes invasion into surrounding tissue, transit into blood or lymphatic fluid, and proliferation. This process largely relies on cell motility, which could be therapeutically inhibited to prevent metastasis and dramatically reduce death and suffering from prostate cancer.

Genistein (4',5,7-trihydroxyisoflavone) is a small molecule found in high amounts in soy products that has been implicated as having a variety of anti-tumor and anti-metastatic effects. With funding from an FY13 PCRP Laboratory - Clinical Translation Award, Dr. Bergan and his team are performing comprehensive preclinical studies using a previously developed derivative of genistein, KBU2046. KBU2046 was originally discovered by making chemical modifications to genistein and then selecting for only those genistein derivatives that inhibited human prostate cancer cell motility and invasion. Dr. Bergan and his colleagues have demonstrated that KBU2046 is a highly selective and potent small molecule that decreases human prostate cancer cell motility, metastasis, and bone destruction and prolongs survival in animal models of prostate cancer. KBU2046 can be taken orally and does not hinder the efficacy of cytotoxic chemotherapeutic agents used to treat prostate cancer.

Dr. Bergan's team is currently performing the toxicology studies necessary for submitting an Investigational New Drug application to the FDA, and successful completion of these preclinical studies will help move this first-in-class compound targeting cell motility from the laboratory into future prostate cancer clinical trials. Dr. Bergan hopes that KBU2046 could be used to treat patients with high-risk localized prostate cancer to augment surgery or radiation therapy in order to prevent or delay initial development of metastatic disease. Additionally, KBU2046 could be used to treat patients with advanced metastatic prostate cancer in combination with existing therapies to prevent further disease spread. Thus, inhibition of cell motility by KBU2046 may potentially have a major impact on prostate cancer lethality by blocking a cellular process that drives the major cause of death—metastasis.



"The CDMRP Prostate Cancer Research Program is a rigorous peer review process that funds groundbreaking and high-impact research on the understanding, prevention and treatment of prostate cancer. It is truly a privilege to be part of this incredible research program."

Parvesh Kumar, M.D., Professor and Chair, Department of Radiation Oncology; Director, Cancer Program; Vice Dean of Research; Principal Investigator, Mountain West IDeA Clinical and Translational Research–Infrastructure Network, University of Nevada, Las Vegas School of Medicine

Kiran Mahajan

Nupam Mahajan

Inhibition of ACK1 to Overcome Drug Resistance in Prostate Cancer

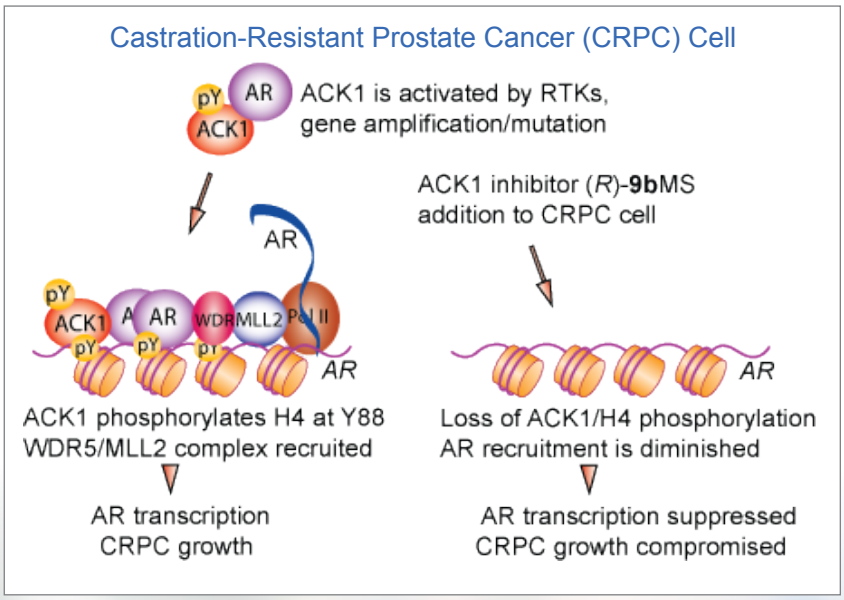
Kiran Mahajan, Ph.D., H. Lee Moffitt Cancer Center and Research Institute, University of South Florida

Nupam Mahajan, Ph.D., H. Lee Moffitt Cancer Center and Research Institute, University of South Florida

The AR is a paramount player in both the initiation and progression of prostate cancer. Cancer cells initially respond to treatment with anti-androgen drugs, such as enzalutamide, but often become resistant and progress to a lethal state of disease called mCRPC. For these types of patients whose prostate cancer no longer responds to anti-androgen drugs, novel therapies are greatly needed. To develop new therapies, researchers have studied mechanisms of therapeutic resistance, and extensive studies have established that one way cancer cells can bypass the effect of anti-androgens is by substantially increasing AR levels, although this mechanism is not fully understood.

To identify a new therapeutic strategy to tackle this problem, a team of researchers led by Drs. Kiran Mahajan and Nupam Mahajan looked for novel AR interacting partners and identified the protein, ACK1, which is frequently upregulated in mCRPC. With support from FY11, FY12, and FY14 PCRP Exploration – Hypothesis Development Awards to both investigators, they found that ACK1 is recruited by AR to increase AR protein production, even in the presence of enzalutamide, through a novel histone H4 phosphorylation event called Tyrosine 88 phosphorylation. Realizing the significance of this observation, they developed a novel small molecule inhibitor called (R)-9bMS that targets ACK1 and showed that it suppresses AR and its variant AR-V7 expression, culminating in inhibition of growth of enzalutamide-resistant tumors in mice.

The promotion of AR protein production in the presence of enzalutamide through ACK1-mediated histone phosphorylation is a new finding in prostate cancer. More importantly, the new inhibitor, (R)-9bMS, that the research team has developed could become a new therapeutic modality, especially for those patients that are not initially responsive to enzalutamide or have developed resistance to it. The H. Lee Moffitt Cancer Center has patented this discovery and licensed this compound for its development as a cancer drug. It is expected that this compound will become available for early clinical trials in the next 1 to 2 years.



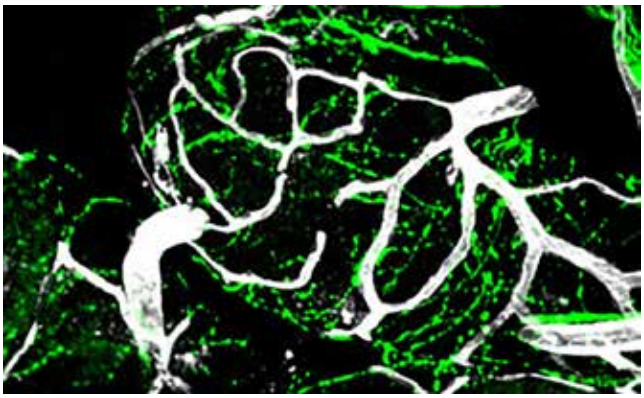
ACK1 enters the nucleus and phosphorylates histone H4 at Tyr88 upstream of the AR transcription start site, leading to the WDR5/MLL2 complex-mediated increase of AR transcription. Inhibition of ACK1 reverses the phosphorylated Tyr88-H4 marks and reduces AR and AR-V7 levels to mitigate castration-resistant prostate tumor growth.

Autonomic Nerves Drive Prostate Cancer Growth, Invasion, and Metastasis

Paul Frenette, M.D., Albert Einstein School of Medicine

Localized prostate cancer is usually slow-growing, but if the cancer begins to invade and metastasize to other parts of the body, then the disease quickly becomes lethal. If researchers can better understand the process of how invasion and metastasis occurs, it is possible to develop new treatments to better control prostate cancer and render it a non-threatening disease. Dr. Frenette, then at Mount Sinai School of Medicine, and his colleagues discovered an unexpected role for the nervous system in the invasion and metastasis of prostate cancer. Funded by an FY06 PCRP Idea Development Award, Dr. Frenette further investigated this novel discovery, which has led to a better understanding of how the autonomic nervous system (ANS) is involved in the regulation of prostate cancer development and metastasis.

The ANS is responsible for regulating body functions such as heart rate, respiratory rate, urination, and sexual arousal. The two main divisions of the ANS are the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS), which work together to carefully regulate internal body processes. The SNS consists of adrenergic nerves and is primarily responsible for stimulating body processes, while the PNS consists of cholinergic nerves and is primarily responsible for inhibiting those processes. Interestingly, Dr. Frenette's group was able to develop a new understanding of how these two divisions of the ANS play complementary roles in the growth and development of prostate cancer and its ability to infiltrate and migrate into surrounding tissue. Using mouse models of prostate cancer, Dr. Frenette discovered that adrenergic signals from the SNS control the initial phases of cancer development by promoting tumor cell survival, while the cholinergic signals of the PNS play important roles in tumor cell invasion and metastasis. A retrospective blinded analysis of prostate cancer specimens from 43 patients revealed that increased densities of sympathetic and parasympathetic nerve fibers in tumor and surrounding normal tissue were associated with poor clinical outcomes. In further studies, Dr. Frenette evaluated the interaction of neural networks within the tumor microenvironment and vasculature and found that denervation (loss in nerve supply) of adrenergic nerves prevented the development of blood vessels and, consequently, prostate cancer growth. They also discovered that expression of the beta2 adrenergic receptor (Adrb2) acted as a nerve-dependent angiogenic "switch" in endothelial cells. If this switch is turned off by deleting Adrb2, a cascade of events, including changes in Coa6 expression and metabolism, leads to inhibited angiogenesis and tumor growth. These results suggest a novel interplay between neural signals, tumor metabolism, and angiogenesis.



Sympathetic-nerve fibers (green) are closely intertwined with blood vessels (white). Norepinephrine released by nerve fibers stimulates vessel proliferation that fuels tumor growth.

Dr. Frenette's work suggests that blocking Adrb2 through a non-specific beta blocker in prostate cancer patients could inhibit tumor growth. Now located at Albert Einstein School of Medicine, Dr. Frenette and his clinical collaborators at Montefiore Medical Center have begun a pilot study in prostate cancer patients who are receiving a non-selective beta blocker after their diagnostic biopsies and prior to prostatectomy. They will evaluate the impact of the beta blocker on tumor proliferation, cell death markers, and innervation. This pilot study, titled "Beta adrenergic receptor blockade as a novel therapy for patients with adenocarcinoma of the prostate," is led by Benjamin Gartrell, M.D., and can be found on the ClinicalTrials.gov website (NCT02944201).

Circulating Tumor Cell Analysis as a Treatment-Specific Biomarker for Prostate Cancer

Howard Scher, M.D., Memorial Sloan Kettering Cancer Center

Daniel Danila, M.D., Memorial Sloan Kettering Cancer Center

In recent years, drug development for mCRPC has shifted toward a precision medicine approach, in which the choice of treatment is based on the biologic profile of an individual patient's tumor. However, this requires the ability to assess the molecular basis of a patient's cancer using an analytically valid biomarker assay at the time of treatment, which is not currently available. The PCRP awarded Dr. Howard Scher and his research team at Memorial Sloan Kettering Cancer Center an FY12 Transformative Impact Award to implement a systematic approach to biomarker development that begins with an analytically valid assay, followed by a clinical validation program.

Dr. Scher's team began by focusing their efforts on developing a biomarker assay to reliably measure the level of a variant androgen receptor protein, AR-V7, which has been associated with poor clinical prognosis and resistance to next-generation androgen receptor signaling inhibitors (ARSi), such as enzalutamide and abiraterone. With support from the Transformative Impact Award, as well as an FY08 PCRP Physician Research Training Award to Dr. Daniel Danila, Dr. Scher's team investigated the correlation between the level of detectable AR-V7 protein in cancer cells circulating in a patient's bloodstream, called circulating tumor cells (CTCs), with clinical progression by measuring changes in PSA and time to radiographic progression free and overall survival. The research team analyzed CTCs in patients treated with either taxane-based chemotherapy or ARSi at the point in their disease management where a change in therapy was needed. These studies demonstrated that mCRPC patients expressing AR-V7 protein, specifically localized in the nucleus of CTCs, responded well to taxane-based chemotherapy. Conversely, the presence of both nuclear and non-nuclear localization of AR-V7 protein corresponded to patients that responded well to ARSi inhibitors. These results suggest that AR-V7 protein localization is a key factor in predicting positive response to taxane-based treatment and can be used as a predictive biomarker to guide treatment selection men with mCRPC.

Dr. Scher's group also utilized the PCRP-funded PCCTC to evaluate the correlation between CTC phenotypic heterogeneity, or the amount of variation in both gene expression and morphology, and patient response to either taxane or ARSi therapy. They found that, for mCRPC patients whose CTCs lacked AR-V7 expression, low CTC phenotypic heterogeneity was associated with better overall survival in patients treated with ARSi, whereas high CTC heterogeneity was associated with better overall survival in patients treated with taxane chemotherapy. This work, therefore, provided evidence that phenotypic heterogeneity may be informative for selecting treatments for patients without the AR-V7 splice variant.

Collaborations between Dr. Scher and industry partners, Epic Sciences and Genomic Health, has resulted in an AR-V7 liquid biopsy test (Oncotype DX AR-V7 Nucleus Detect Test), which is now commercially available. Efforts to demonstrate the clinical utility of using CTC phenotypic heterogeneity at the single-cell level as a predictive biomarker for treatment decisions are still ongoing; a larger cohort study is planned, and assessments of longitudinal and kinetic changes over time in response to therapy are ongoing, both within the context of mCRPC clinical decisions and outside of prostate cancer. Separately, a PCCTC-led prospective clinical trial testing the ability of CTC AR-V7 mRNA and nuclear-specific AR-V7 protein in matched samples to predict treatment response (NCT02269982) is ongoing.

The processes established by Dr. Scher's Transformative Impact Award have allowed his team to continue working on validating assays for additional prostate cancer biomarkers. These assays have the potential to advance personalized medicine by reducing patients' exposure to ineffective, potentially toxic, and costly treatments, and they may also impact the development of new therapies by enabling clinical trials enriched for patients most likely to respond.

Drs. David Jarrard, Kyle Richards, and Vincent Cryns

Combining Metformin with Androgen Deprivation Therapy to Treat Advanced Prostate Cancer

David Jarrard, M.D., University of Wisconsin

Vincent Cryns, M.D., University of Wisconsin

Progression to castration-resistant prostate cancer (CRPC), the potentially lethal form of prostate cancer, can result after the initiation of androgen deprivation therapy (ADT). One underutilized therapeutic strategy that has the potential to dramatically improve outcomes is eradicating the persistent cancer cells that remain after ADT and likely play a key role in the development of CRPC. Data from the laboratories of Drs. David Jarrard and Vincent Cryns at the University of Wisconsin suggest that these resistant cancer cells adopt a senescent phenotype in which they stop growing, but still survive and secrete substances to promote tumor growth. They discovered that these cells have certain characteristics that may make them susceptible to drugs that affect metabolism. As such, they predicted that metformin, which is a safe, low-cost drug with minimal side effects used to treat diabetes, would eliminate these metabolically active cancer cells remaining after ADT and improve cancer outcomes.

With funding from an FY15 PCRP Idea Development Award, Drs. Jarrard and Cryns and their laboratories are conducting experiments in cellular and animal models to determine the efficacy and mechanisms involved in combining metformin with ADT. They have also examined this combination therapy, in conjunction with co-investigator Dr. Kyle Richards, by using existing electronic health record data in a large national Department of Veterans Affairs database of men with prostate cancer who were treated with ADT. Some of these men were also treated with metformin for diabetes or pre-diabetes and some were not. Through this, they found that men with prostate cancer who were treated with both ADT and metformin had improved survival compared to men who only received ADT. Metformin also reduced the risk of cancer spreading to the bone.

Definitive data in a clinical trial is required before this approach could be clinically used to treat prostate cancer patients. Plans for such a trial are ongoing, which would further define exactly which patients were most likely to benefit from this approach. Because metformin is an inexpensive drug that is already FDA-approved for diabetes treatment, it has the potential to move into the clinic quickly and help improve treatment outcomes for men with prostate cancer undergoing ADT.

"The PCRP promotes results-oriented cutting edge research into prostate cancer's origin, diagnosis, treatment, and post-treatment care without profit motive encumbrances possible in a civilian setting. Military operations are also results-oriented. So, placing this program within the military structure makes perfect sense. Since we in the military are a reflection of our population at large, we will reflect similar health conditions. However, we in the military are charged with maintaining a viable fighting force, making it essential that the military is able to effectively deal with the health conditions of its personnel. The PCRP is one of those tools that help maintain a healthy fighting force. I'm proud to be a military member--retired--and glad for the opportunity to contribute the PCRP's success."

Mr. Don Triplett, Prostate Cancer Survivor and Research Advocate, US Too International

Clinical Implications for Long Non-coding RNAs in Prostate Cancer

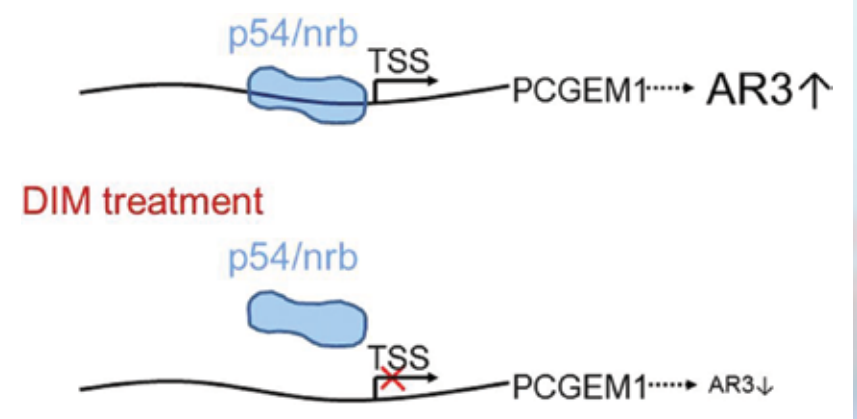
Before the discovery of non-coding RNA genes in cancer, the search for novel genes that drive the development of cancer was focused mainly on protein-coding genes, called messenger RNA, which consists of only 2% of the human genome. During the last decade, advances in next-generation sequencing enabled the discovery of long non-coding RNA (lncRNA) transcripts, a new category of molecules that function in a spatiotemporal manner in normal tissue and cancer development. LncRNAs have been implicated in the development and progression of a variety of cancers, including prostate cancer. However, to date, only a hand full of lncRNAs have been characterized and studied in prostate cancer, and their clinical utility and therapeutic potential remain unknown. The PCRP's investment in this innovative area of research has led to some promising results that have the potential for future impacts on patients.

Dr. Chi Dang

Chi Dang, M.D., Ph.D., and colleagues at the **University of Pennsylvania** are investigating the potential of lncRNA signatures to predict clinical outcomes for prostate cancer patients. With support from an FY14 PCRP Idea Development Award, they discovered that the lncRNA DANCR is highly elevated in prostate cancer tumors and is essential for prostate cancer cell line growth. Additionally, they found that it functions through suppressing p21, a gene that inhibits the proliferation of cancer cells. Future studies aim to determine the clinical relevance of these findings by assessing DANCR expression in prostate biopsy samples and prostatectomy tissues, which will indicate whether DANCR could serve as a novel biomarker for prostate cancer progression risk.

Dr. Yin-Yuan Mo

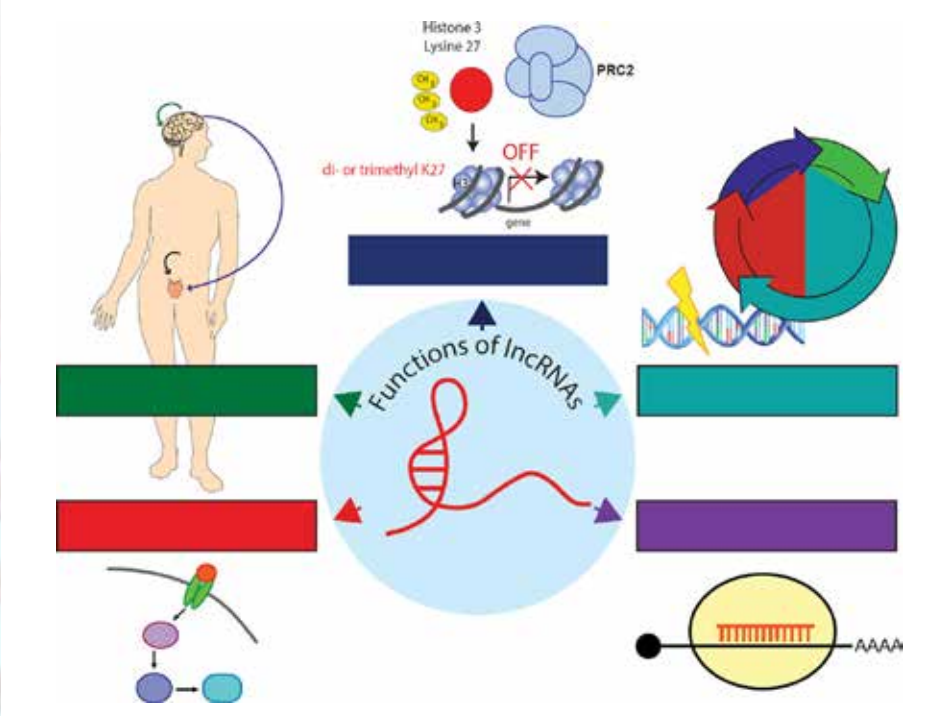
Yin-Yuan Mo, Ph.D., at the **University of Mississippi** explored how lncRNAs are involved in alternative splicing of AR and contribute to castration-resistance (resistance to AR therapy). With support from FY11 and FY14 PCRP Exploration-Hypothesis Development Awards, Dr. Mo and his colleagues identified PCGEM1 as a major lncRNA that is upregulated in prostate cancer specimens and castration-resistant cell lines and showed that PCGEM1 is induced by androgen deprivation. Additionally, they found that 3,3'-Diindolylmethane (DIM), a known chemoprevention agent in Phase 2 clinical trials for prostate cancer and other malignancies, is capable of suppressing PCGEM1 expression in prostate cancer mouse models. This suggests that PCGEM1 may be a new therapeutic target for CRPC.



A proposed model for p54/nrb-mediated regulation of PCGEM1. Once cells are treated with DIM, DIM prevents p54/nrb from binding to the PCGEM1 promoter and decreases the expression of PCGEM1, thus resulting in the down-regulation of AR3. TSS: transcription start site.

Dr. Rohit Mehra

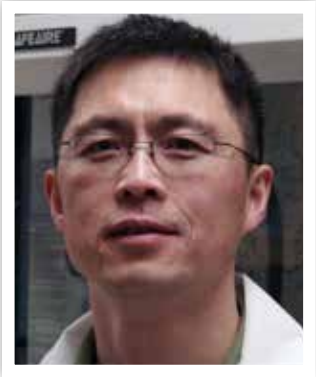
At the **University of Michigan**, investigators are also searching for novel lncRNAs that could be clinically relevant for prostate cancer patients. With support from an FY15 PCRP Idea Development Award, **Rohit Mehra, M.D.,** and colleagues used RNA sequencing to profile the transcriptome of more than 100 prostate cancer tissues and cell lines and found that roughly 20% of RNA transcripts in prostate cancer represent novel, uncharacterized lncRNA genes. One lncRNA of great interest to this group is PRCAT47 (a.k.a. ARLNC1). They found that PRCAT47 is expressed in a prostate tissue-specific manner and has elevated expression in localized and metastatic prostate cancer. They also observed that loss of this lncRNA inhibits cell proliferation and affects androgen receptor (AR) signaling, a crucial pathway in prostate cancer cell survival. Their most recent results have demonstrated that PRCAT47 mediates AR post-transcriptionally, and lncRNA-interacting proteins are likely to be involved in this regulation process, confirming that PRCAT47 has the potential to serve as a diagnostic prostate cancer biomarker.



LncRNAs play a crucial role within major areas of cancer progression and metastasis. From: Long noncoding RNAs in cancer: from function to translation.

Long noncoding RNA (lncRNAs) mediate several cancer-associated processes, including epigenetic regulation, DNA damage and cell cycle control, microRNA (miRNA) silencing, signal transduction pathways, and hormone-driven disease.

Taken together, this recent research from three separate PCRP-funded laboratories has contributed to increased knowledge of lncRNAs and their importance in prostate cancer biology. Specifically, this work has demonstrated that newly discovered lncRNAs, such as DANCR and PRCAT47, have the potential to be novel biomarkers for prostate cancer patients. Additionally, lncRNAs such as PCGEM1 may serve as important therapeutic targets for treating patients with aggressive, CRPC. While further investigation is needed to confirm these results and translate this work, the PCRP's investment in this novel line of research has helped pave the way for future advancements.



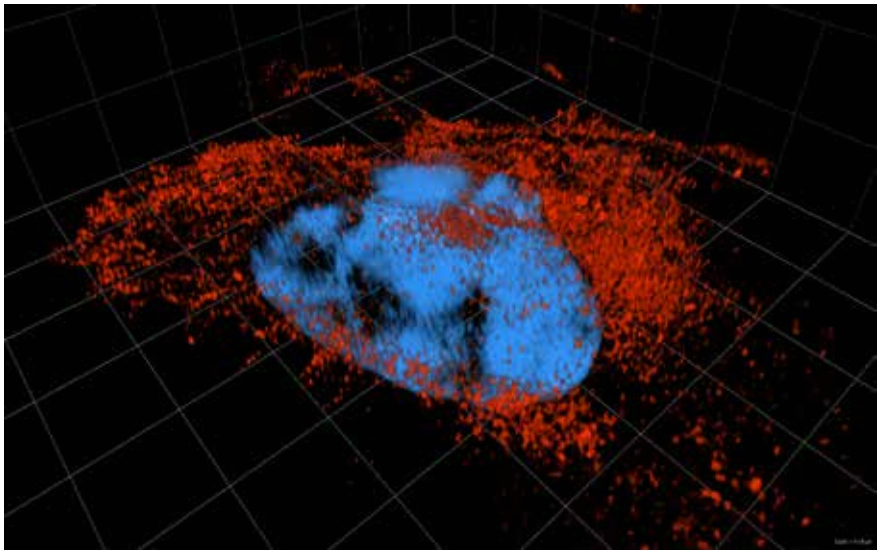
A New Positron Emission Tomography (PET) Imaging Probe for Detection of Aggressive Prostate Cancer

Jianghong Rao, Ph.D., Stanford University

PET is a nuclear medicine functional imaging technique that is used to observe metabolic processes in the body as an aid to diagnose disease. While PET has revolutionized the clinical treatment of prostate cancer with the ability to detect the location of primary and metastatic lesions anywhere in the body, the current PET reagents (e.g., 18F-FDG) rely on cellular uptake and have limited utility due to the slow-growing nature and low metabolic activity of prostate cancer cells. Therefore, innovations in the area of biomarkers and PET reagent technology may hold the key for the early detection of aggressive prostate cancer and metastatic lesions. With funding from an FY13 PCRP Idea Development Award, Dr. Rao employed a novel chemistry (enzyme-triggered self-assembly of radiolabeled small molecule tracers into nanoparticles) developed in his laboratory to create a highly specific PET–mediated imaging agent for early detection of prostate cancer and subsequent metastases.

Methionine aminopeptidase II (MetAP2) is an enzyme that catalyzes the removal of the N-terminus methionine residue from nascent proteins and is thought to play a key role in angiogenesis (i.e., the growth of new blood vessels that help feed tumor growth and promote metastasis) and hence the progression of advanced prostate cancer. Because of its crucial role, MetAP2 is a drug target for potent angiogenesis inhibitors used for cancer therapy. Dr. Rao hypothesized that MetAP2 could also serve as a novel diagnostic biomarker for prostate cancer. Using immunohistochemistry and tissue microarrays containing 513 prostate cancer patient biopsies, Dr. Rao and his team at Stanford University demonstrated that MetAP2 is overexpressed in prostate cancer, with higher enzyme levels expressed in higher-grade cancerous tissues. To exploit this, Dr. Rao designed and synthesized a molecular imaging probe, called 18F-M-SNAP (MetAP2 sensitive nano-aggregation probe) that is activated in the presence of MetAP2 to form large self-aggregates or nanoparticles. These nanoparticles are trapped and activated inside cancer cells where MetAP2 expression is high, allowing for highly selective tumor cell imaging. Dr. Rao demonstrated, using 18F-M-SNAP in an animal model of prostate cancer, that PET imaging can readily detect the uptake and accumulation of MetAP2 in prostate tumors, supporting the probe's diagnostic potential in PET imaging.

These results highlight MetAP2 as a promising imaging biomarker of prostate cancer that can, for the first time, be detected by PET imaging using Dr. Rao's newly developed 18F-M-SNAP probe. MetAP2 PET imaging may provide a highly sensitive and noninvasive approach for prostate cancer detection, staging, and monitoring of therapeutic response. This innovative PET reagent technology, which relies on enzyme presence rather than metabolic activity, may hold the key for the early detection of aggressive prostate cancer and metastasis.



Aggregated particles mediated by the activity of MetAP2 in a single PC3 cancer cell (blue is DAPI stained nucleus; red is aggregated particles).

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 shown here in the clinical pipeline, with additional details available on pages 23-27.

Focus Area	Agent/Technique	Preclinical	Phase I/II	Phase III	To Patients
Mechanisms of Resistance and Response	N-Cadherin monoclonal antibodies				
	3βHSD1 mutation				

Focus Area	Agent/Technique	Preclinical	Phase I/II	Phase III	To Patients
Imaging	Multiadaptive Plan Intensity-Modulated Radiation Therapy (IMRT)				
	T2-weighted prostate Magnetic Resonance Imaging (MRI) at 7 Tesla (T) using a simplified external transmit receive coil array				
	Multichannel Image-Guided Robotic Assistant for Brachytherapy (MIRAB)				
	Electrical Impedance Spectroscopy (EIS) for noninvasive detection of prostate tumors				
	124I-anti-Prostate Stem Cell Antigen (PSCA) A11 minibody				
	PMSA-based PET Imaging Agent				
	MRI-guided robotic device for real-time needle placement in prostate biopsy sample retrieval				
	Fluorine-18 Fluorocholine (FCH) PET				
	Restriction Spectrum Imaging (RSI)-MRI				
	68 Ga DOTA Bombesin (68Ga-RM2)				
	MRI-Based Treatment Planning for Radiotherapy				
	Elekta Synergy				

Focus Area	Agent/Technique	Preclinical	Phase I/II	Phase III	To Patients
Chemotherapy	Gamitrinib				
	Entinostat (MS-275)				
	Phenelzine sulfate				

Focus Area	Agent/Technique	Preclinical	Phase I/II	Phase III	To Patients
Combination Therapy	Veliparib (ABT888) plus radiation				

Focus Area	Agent/Technique	Preclinical	Phase I/II	Phase III	To Patients
Hormonal Therapy	NEW Seviteronel (VT-464)				
	Mifepristone plus enzalutamide				
	N-terminal domain inhibitor (EPI-506)				
	3,3'-diindolylmethane (DIM)				
	ZYTIGA® Abiraterone Acetate				
	Xtandi® (enzalutamide)				
	NEW Erleada™ (Apalutamide)				

Focus Area	Agent/Technique	Preclinical	Phase I/II	Phase III	To Patients
Immunotherapy	MDA-7/IL-24				
	NEW Adenoviral PSA Vaccine				
	Lm-PCaVx (ADU-741)				
	PSA 146-154 peptide vaccine				
	BP-GMAX-CD1				
	DNA vaccine encoding Prostatic Acid Phosphatase (PAP) (pTVG-HP)				
	MEDI6383 (OX40 Antibody)				
	Ipilimumab				

Focus Area	Agent/Technique	Preclinical	Phase I/II	Phase III	To Patients
Radiotherapy	Inverse planning technique for prostate IMRT				
	177Lu-J591				

Focus Area	Agent/Technique	Preclinical	Phase I/II	Phase III	To Patients
Targeted Therapy	J591- Duocarmicin conjugate				
	NEW KBU2046				
	ACK1 Inhibitor				
	NEW Indomethacin plus Enzalutamide				
	C-209				
	G-202				
	BET Inhibitor (ZEN003694)				
	NEW Durvalumab plus Olaparib				
	NEW Sunitinib				
	XGEVA® (denosumab)				
	Velcade® (PS-341)				

Focus Area	Agent/Technique	Preclinical	Phase I/II	Phase III	To Patients
Biomarkers	NEW AR-V7 mRNA assay				
	NuSAP1 Marker (Prolaris, Decipher assays)				
	NEW Nuclear AR-V7 Protein CTC Assay				

Research Area	Agent/ Technique	Principal Investigator Award Mechanism	Description
Preclinical			
Imaging	Multiadaptive Plan (MAP) intensity-modulated radiation therapy (IMRT)	Ping Xia Idea Development Award	Adaptive radiotherapy technique that takes into account the independent motion of both the prostate and pelvic lymph nodes, optimizing the plan to provide full dose to both treatment areas while significantly reducing side effects associated with radiation to normal tissue.
Imaging	T2-weighted prostate magnetic resonance imaging (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.
Imaging	Multichannel Image-Guided Robotic Assistant for Brachytherapy (MIRAB)	Tarun Podder New Investigator Award	This device is able to simultaneously insert 16 small radioactive sources or "seeds" into the prostate while also securing them in place. Preclinical testing found that MIRAB can position the seeds with sub-millimeter accuracy. This has the potential to reduce side effects such as edema, while also reducing the operating time.
Imaging	Electrical Impedance Spectroscopy (EIS) for noninvasive detection of prostate tumors	Ryan Halter Prostate Cancer Training Award New Investigator Award Idea Development Award Synergistic Idea Development Award	This study 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.
Mechanisms of Resistance and Response	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.
Therapy (Combination Therapy)	Veliparib (ABT888) plus radiation	Phyllis Wachsberger Exploration Hypothesis Development Award	A new class of anti-cancer compound (PARP inhibitors), was shown in animal models to sensitize prostate cancer tumors to radiation, thus making the radiation more effective at reducing tumor growth.
Therapy (Immunotherapy)	MDA-7/IL-24	Paul Fisher and Xiang-Yang Wang Synergistic Idea Development Award"	Preclinical development of 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.
Therapy (Radiotherapy)	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.
Therapy (Targeted Therapy) NEW	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 cGMP production. The PCRP-supported preclinical studies required for Investigational New Drug (IND) application submission are underway.
Therapy (Targeted Therapy)	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 has also been licensed for development as a cancer drug.

Research Area	Agent/ Technique	Principal Investigator Award Mechanism	Description
Therapy (Targeted Therapy)	J591- duocarmicin 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.
Phase I / II			
Biomarkers NEW	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 (CTCs) 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.
Imaging	124I-anti-PSCA A11 minibody	Robert Reiter Laboratory Clinical Transition Award	A radiolabeled prostate stem cell antigen (PSCA) antibody fragment (minibody) was developed for positron emission tomography (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 more closely the diagnosis and treatment of this disease.
Imaging	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 imaging agent is in Phase I/II clinical trials to evaluate its utility in detecting advanced prostate cancer.
Imaging	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.
Imaging	Fluorine-18 Fluorocholine (FCH) PET	Sandi Kwee New Investigator Award	Used to detect cancer by measuring the tissue metabolism of FCH, a substrate that is preferentially metabolized by cancer cells. This technique, combined with CT scanning, can be used for whole-body detection of prostate cancer and to improve guidance of radiation therapy. Phase I/II 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.
Imaging	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 California, San Diego.
Mechanisms of Resistance and Response	3βHSD1 mutation	Zhenfei Li Nima Sharifi Physician Research Training Award	Discovered a mechanism of resistance to androgen deprivation therapy (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 II clinical trial studying 3βHSD genotype and the non-steroidal CYP17A1 inhibitor, apalutamide, is in progress.
Therapy (Chemotherapy)	Gamitrinib	Dario Altieri Laboratory Clinical Transition Award	First-in-class mitochondrial-targeted small molecule Hsp90 inhibitor with potent anti-cancer 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 I clinical trial of Gamitrinib is now planned in patients with advanced and metastatic prostate cancer.
Therapy (Chemotherapy)	Phenelzine sulfate	Jean Shih Idea Development Award	Monoamine oxidase A (MAOA) inhibitor slows prostate cancer tumor growth and metastasis to the bone. FDA-approved for the treatment of depression, phenelzine sulfate is currently being tested in a Phase II clinical trial on non-metastatic, recurrent prostate cancer.

Research Area	Agent/ Technique	Principal Investigator Award Mechanism	Description
Therapy (Chemotherapy)	Entinostat (MS-275)	Roberto Pili New Investigator Award	A histone deacetylase inhibitor was shown to halt the growth and proliferation of prostate cancer in vitro and in vivo. In a small Phase I study, a combination of entinostat with 13-cis retinoic acid was shown to be reasonably well tolerated. Currently, there are ongoing Phase II trials in Hodgkin's lymphoma, advanced breast cancer (in combination with aromatase inhibitors), and metastatic lung cancer (in combination with erlotinib).
Therapy (Hormonal Therapy) NEW	Seviteronel (VT-464)	Howard Scher Clinical Consortium Award	Seviteronel (VT-464), a next-generation androgen synthesis inhibitor, is currently in PCCTC-led early clinical development. A Phase II clinical trial is ongoing in patients with CRPC with rising PSA levels during treatment with enzalutamide, abiraterone, or both. Seviteronel has been granted fast-track designation for patients with CRPC by the FDA.
Therapy (Hormonal Therapy)	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 I and II clinical trials to study the combination of Mifepristone, a glucocorticoid receptor (GR) blocker, in addition to enzalutamide, an AR blocker, to determine whether this combination treatment can overcome ADT resistance in patients with CRPC.
Therapy (Hormonal Therapy)	3,3'-diindolylmethane (DIM)	Stephen Safe Idea Development Award Yin-Yuan Mo Exploration - Hypothesis 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 I and II clinical trials.
Therapy (Hormonal Therapy)	N-terminal domain inhibitor (EPI-506)	Marianne Sadar and Stephen Plymate Idea Development Award Synergistic Idea Development Award	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 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 filing expected to occur in early 2019.
Therapy (Immunotherapy) NEW	Adenoviral PSA Vaccine	David Lubaroff Clinical Trial Award	An adenoviral PSA vaccine has been tested in two Phase II clinical trials in patients with recurrent 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.
Therapy (Immunotherapy)	Lm-PCaVx (ADU-741)	Dirk Brockstedt Laboratory Clinical Transition Award	A listeria-based vaccine designed to stimulate an immune response to three prostate cancer antigens. An open-label Phase I clinical trial to test the safety and immunogenicity of JNJ-64041809 in patients with mCRPC was initiated in 2015.
Therapy (Immunotherapy)	PSA 146-154 peptide vaccine	David Peace Idea Development Award Phase II Idea Development Award	PSA vaccine 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.
Therapy (Immunotherapy)	BP-GMAX-CD1	Kevin Slawin Idea Development Award	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. Prelimiary results of a Phase I/II trial in patients with advanced, androgen-independent prostate cancer demonstrated anti-tumor activity with PSA declines and tumor regression.
Therapy (Immunotherapy)	DNA vaccine encoding Prostatic Acid Phosphatase (pTVG-HP)	Doug McNeel Clinical Trial Award Laboratory Clinical Transition Award Postdoctoral Traineeship Award	Shown to stimulate an immune response to PAP, a protein specific to prostate cancer cells. This vaccine is currently being tested in Phase I/II clinical trials in combination with anti-PD1 antibody treatment in patients with both early- and late-stage prostate cancer.
Therapy (Immunotherapy)	MEDI6383 (OX40 Antibody)	Andrew Weinberg Laboratory Clinical Transition Award	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 Ib clinical trial in partnership with Medimmune has been completed.

Research Area	Agent/ Technique	Principal Investigator Award Mechanism	Description
Therapy (Radiotherapy)	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 II clinical trial funded by the PCRP.
Therapy (Targeted Therapy) NEW	Indomethacin plus Enzalutamide	Chong-xian Pan Allen Gao Christopher Evans Impact Award - Clinical Trial - Partnering PI Option"	A Phase I/II 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.
Therapy (Targeted Therapy)	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 Ib clinical trials of childhood glioma and ovarian cancer.
Therapy (Targeted Therapy)	G-202	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 II clinical trial of G-202 in patients with localized, high-risk prostate cancer prior to prostatectomy has been completed.
Therapy (Targeted Therapy)	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 I clinical trial sponsored by Zenith Epigenetics. A Phase I/II trial testing the combination of ZEN-003694 and enzalutamide in patients with mCRPC is currently recruitng.
Phase II			
Therapy (Targeted Therapy) NEW	Durvalumab plus Olaparib	Fatima Karzai Physician Research Award	Preliminary results of a pilot clinical study suggest that a combination of the PARP inhibitor, olaparib, and the anti-PDL-1 antibody, durvalumab, in men with mCRPC dramatically reduces PSA levels and measureable metastatic lesions, regardless of mutational status. An expanded Phase II clinical trial of olaparib and durvalumab is currently in development for men with mCRPC following enzalutamide or abiraterone treatment.
Phase II/III			
Imaging	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.
Phase III			
Therapy (Immunotherapy)	Ipilimumab	Eugene Kwon Clinical Trial Award	A monoclonal antibody that activates the immune system is FDA-approved for the treatment of melanoma. It was shown to enhance response to ADT, and a Phase III clinical trial in men with metastatic prostate cancer who have not received chemotherapy was completed. Ipilimumab is now being tested in combination with other therapies for multiple types of cancer.
Therapy (Targeted Therapy) NEW	Sunitinib	Dror Michaelson Clinical Trial Award	A drug that targets specific growth factor receptors on endothelial and prostate cancer cells. Sunitinib was tested in a Phase II clinical trial of men with advanced prostate cancer and was well-tolerated. Although there were no significant effects on overall survival or PSA levels, serum biomarkers of angiogenesis and metastatic disease declined. A Phase III clinical trial is underway.

Research Area	Agent/ Technique	Principal Investigator Award Mechanism	Description
To Patients			
Biomarkers NEW	Nuclear AR-V7 Protein CTC Assay	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.
Biomarkers	NuSAP1 Marker (Prolaris, Decipher assays)	James Brooks Idea Development Award - Established Investigator	The PCRP funded early work characterizing NuSAP1 over expression 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	MRI-Based Treatment Planning for Radiotherapy	Lili Chen New Investigator Award Idea Development Award	An MRI-based treatment planning protocol for IMRT was developed that specifically targets prostate tumor tissue and avoids damaging normal tissues and organs. This protocol has several advantages over computed tomography (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.
Imaging	Elekta Synergy	David Jaffray Phase II 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, and over 80% of radiation machines sold today are equipped with it.
Therapy (Hormonal Therapy) NEW	Erleada™ (Apalutamide)	Howard Scher Clinical Consortium Award	The PCCTC led the early clinical development (Phase I/II clinical trials) of apalutamide, resulting in a successful Phase III clinical trial, known as SPARTAN. Erleada™, a next-generation androgen receptor signaling inhibitor, is the first anti-androgen therapy approved by the FDA for non-metastatic CRPC patients.
Therapy (Hormonal Therapy)	ZYTIGA® Abiraterone acetate	Howard Scher Clinical Consortium Award	An anti-androgen was FDA-approved for the treatment of men with metastatic CRPC through clinical testing by the PCRP-funded PCCTC.
Therapy (Hormonal Therapy)	Xtandi® (enzalutamide)	Howard Scher Clinical Consortium Award	FDA-approved for the treatment of men with CRPC. It works by blocking androgens and has been shown to significantly delay cancer progression and prolong life.
Therapy (Targeted therapy)	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.
Therapy (Targeted therapy)	Xgeva® (denosumab)	Evan Keller Idea Development Award	An FDA-approved antibody that slows the progression of prostate cancer bone metastases. It blocks the bone resorption protein, RANKL, thus slowing bone loss during cancer treatment. Xgeva® is 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.

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