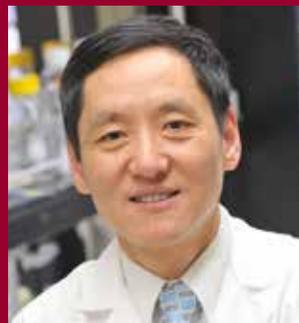
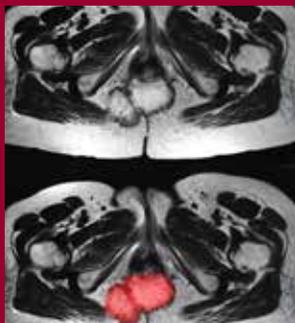
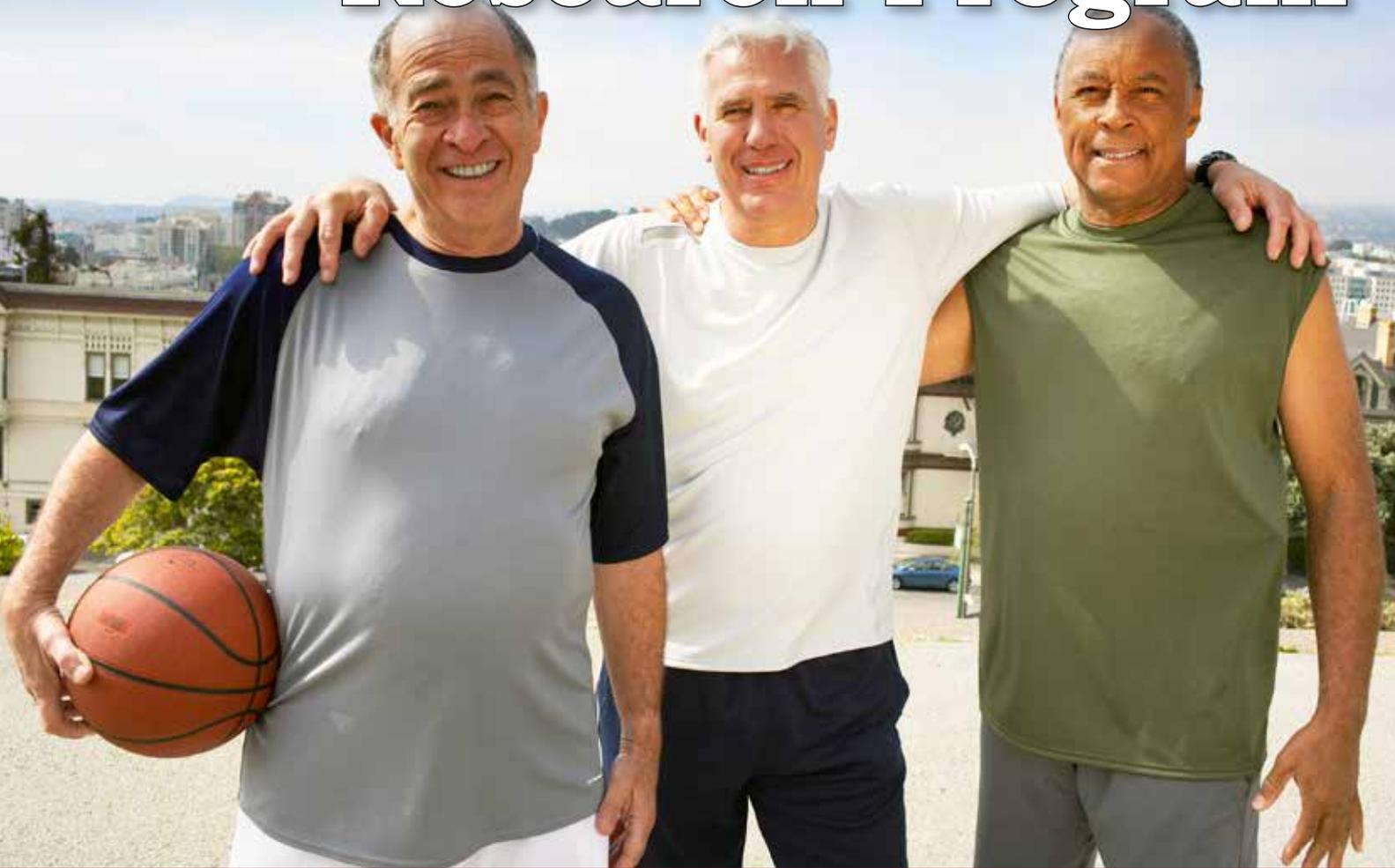


Prostate Cancer Research Program



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 it has received more than \$10 billion (B) in appropriations from its inception through fiscal year 2016 (FY16). 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, with both tiers involving dynamic interaction among scientists and disease survivors. The first tier of evaluation is a scientific peer review of proposals measured against established criteria determining scientific merit. 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.



“As a peer reviewer, I have been always amazed at how many innovative ideas were proposed by such a broad spectrum of researchers, young and old and from all over the U.S. and even other countries. Looking for potential (high-risk) rather than past accomplishments and feasibility (low-risk), the PCRP funding mechanism fills in a void to let creative research happen. Without supporting such unconventional research, progress in prostate cancer therapy and prevention will be lackluster and not at a fast pace that, as consumer reviewers correctly remind me at our study section meetings, is needed now.”

**Ralf Janknecht, Ph.D., Professor of Cell Biology
University of Oklahoma Health Sciences Center**

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 towards 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 \$1.45B in the PCRP, including \$80M in FY16. This unique partnership among Congress, the military, and prostate cancer survivors, clinicians, and scientists has changed the landscape of biomedical study, energizing the research community in conducting 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 men experiencing the impact of the disease

PCRPP PRIORITIES – THE PCRPP SEEKS TO PROMOTE:

- Highly innovative, groundbreaking research
- High-impact research with near-term clinical relevance
- Multidisciplinary, synergistic research
- Translational studies to support the fluid transfer of knowledge between bedside and bench
- Research on patient survivorship and quality of life
- The next generation of prostate cancer investigators through mentored research
- Research on disparities in the incidence and mortality of prostate cancer

FY15 Programmatic Panel Members

Timothy McDonnell, M.D., Ph.D.
(Chair)

University of Texas MD
Anderson Cancer Center

Philip M. Arlen, M.D. (Chair
Emeritus)

Precision Biologics, Inc.

Peter Choyke, M.D., F.A.C.R.
National Cancer Institute

William Dahut, M.D.
National Cancer Institute

Adam Dicker, M.D., Ph.D.
(Chair Elect)
Thomas Jefferson University

James Kiefert, Ed.D.
Us TOO International

Natasha Kyprianou, Ph.D.
University of Kentucky

Daniel Lin, M.D.
University of Washington

Lorelei Mucci, Sc.D., M.P.H.
Harvard School of Public Health

Joel Nowak, M.S.W., M.A.
MaleCare, Inc.

David Quinn, M.B.B.S., Ph.D.,
F.R.A.C.P., F.A.C.P.
University of Southern
California

Marianne Sadar, Ph.D.
University of British Columbia

Westley Sholes, M.P.A.
California Prostate Cancer
Coalition

Virgil Simons, M.P.A.
The Prostate Net

Howard Soule, Ph.D.
Prostate Cancer Foundation

M. Albert Thomas, Ph.D.
University of California, Los
Angeles

Donald Tindall, Ph.D.
Mayo Clinic, Rochester

Moving the Prostate Cancer

PROGRAMMATIC PANEL

PCRP Programmatic Panel members are prominent leaders in prostate cancer research, drawn from the nation's leading research institutions, foundations, and prostate cancer advocacy groups. With diverse expertise, the 17-member panel includes highly knowledgeable scientists, clinicians, and consumer advocates. Each year, the Programmatic Panel determines the most pressing needs and biggest obstacles to achieving better treatment options and improving quality of life for prostate cancer patients, and the program's funding opportunities and investments for the year are designed with these goals in mind.



“PCRP is an amazing effort dedicated to addressing the enormous suffering and impact caused by prostate cancer in our society. The goal of the program is the elimination of prostate cancer by facilitating innovative basic, translational, and clinical research, and stressing the importance of multidisciplinary and synergistic interactions between investigators. Additionally, the DoD PCRP develops young investigators in the field by supporting various training programs. It has been a great privilege to serve with a team of such capable, dedicated, and accomplished individuals on the PCRP Programmatic Panel. Each year, we vigorously assess and refine our priorities and funding strategies in our quest to shorten the time needed to achieve our goal of eliminating death and suffering from this disease.”

Timothy McDonnell, M.D., Ph.D.
The University of Texas MD Anderson Cancer Center
PCRP FY15 Programmatic Panel Chair

Donald Tindall, Ph.D., of the Mayo Clinic at Rochester will be rotating off the panel for FY16 after serving for 8 years. His expertise in the mechanisms of androgen action in prostate cancer has added an abundance of knowledge that has helped further the vision and mission of the PCRP. Dr. Tindall also served as the Chair of the Programmatic Panel in FY10.

For FY16, the PCRP welcomes two new Programmatic Panel members:

Kenneth Pienta, M.D., from
Johns Hopkins University School of Medicine
and

Tarek Bismar, M.D., from the
University of Calgary.

Field Towards Finding A Cure

PCRP OVERARCHING CHALLENGES

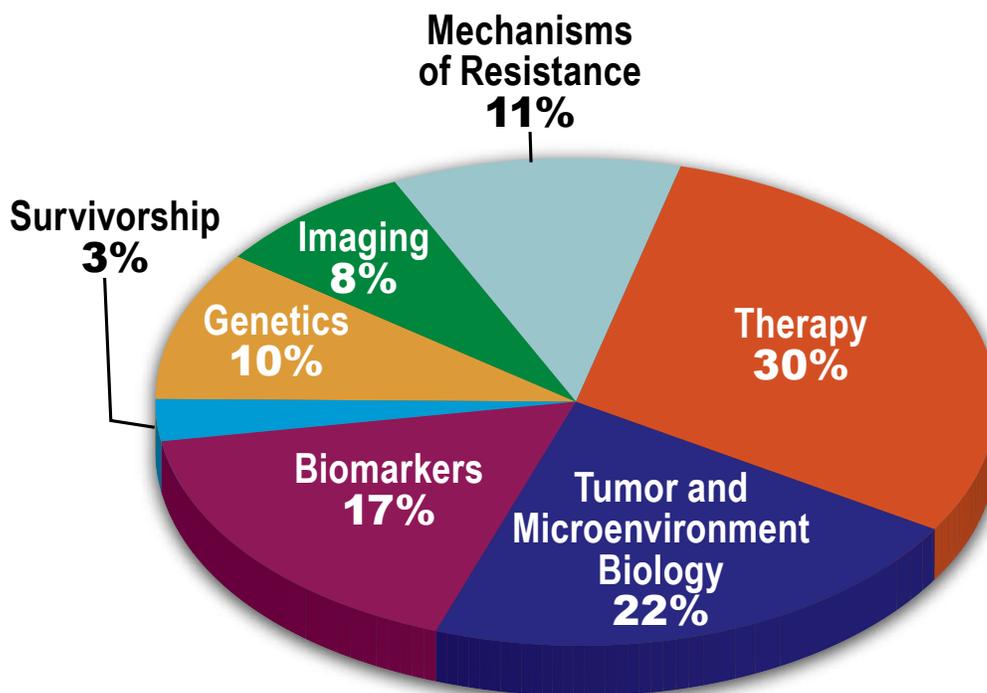
The PCRP was initiated on the predication that identifying better strategies and creating new funding opportunities would facilitate the scientific and clinical communities to move faster towards a cure. While the program invites all ideas that will make a significant impact towards our vision of curing prostate cancer, the PCRP encourages applicants to address specific critical needs for prostate cancer patients:

- ***Distinguishing aggressive from indolent in men newly diagnosed with prostate cancer;***
- ***Developing strategies to prevent progression to lethal prostate cancer;***
- ***Developing effective treatments and addressing mechanisms of resistance for men with high-risk for metastatic prostate cancer;***
- ***Developing strategies to optimize physical and mental health of men with prostate cancer.***

PCRP FOCUS AREAS

The PCRP established seven focus areas to assist researchers in concentrating their projects around program priorities. These focus areas also serve as a mechanism for the program to track whether the PCRP portfolio of funded awards is best aligned with those areas of research that are in greatest need of advancement. The pie chart below shows the number of awards funded in each of the PCRP focus areas since they were introduced in FY09.

FY09–FY15 PCRP Portfolio by Focus Area



Peer Review Participation

Scientists, Clinicians, and Consumer Advocates

Scientists and clinicians with expertise in different scientific disciplines provide expert advice on the scientific merit of proposals. Consumers provide fresh, new perspectives and insights that other panel members may not have, and they bring a sense of urgency to the discussions.



“I am a ten-year prostate survivor, and I’m honored to have served as a consumer reviewer. I have learned we are in an exciting era in the fight against this disease. PCRFP funding is enabling researchers to understand, at the molecular level, the cellular processes that enable the disease to develop and spread. In addition, PCRFP dollars are helping to train the next generation of prostate cancer researchers who I believe will participate in the discovery of a lasting cure for the advanced form of the disease.”

Col Mike Sterling, USAF, (Ret.), US Too International, Inc., Walter Reed

“Participating in the PCRFP program as a scientific reviewer brings humanity to the work that we do. The input of the consumer reviewers is invaluable, as it allows us to focus less on individual research programs and careers, and centers us on the larger community that we ultimately serve.”



Cimona Hinton, Ph.D., Clark Atlanta University



“As a scientist reviewer for last 10 years, and a recipient of the PCRFP funding opportunity, I feel honored and privileged to be a part of the rich scientific community who are working hard to find better methods to fight prostate cancer. Through this review process, I also feel connected to the prostate cancer survivors and learn about the real-life situations. The PCRFP funding mechanism for both basic and clinical sciences is a great way to promote novel ideas for better understanding of the fundamental mechanisms, new therapeutic possibilities, and improved prognostication of the treatment response. The review process is scientifically sound, fair, and in-depth to find the best ideas to promote. The PCRFP award mechanism is also highly beneficial for attracting young investigators to get trained in the prostate cancer field and helping established investigators to pursue their novel ideas. I believe this concerted effort of PCRFP and the research community will lead to improved treatments and quality of life for prostate cancer patients in the near future.”

Ratna Chakrabarti, Ph.D., University of Central Florida

393 Consumers and 1,808 Scientific Reviewers have participated in Peer Review throughout the history of the PCRCP.



“As a physician-scientist, I have been working on prostate cancer for the last 15 years with multiple grant support from DoD PCRCP program since 2003. DoD PCRCP is a wonderful funding agency for prostate cancer research, and I have been serving as the scientist reviewer for this program since 2007. It is a great pleasure and honor to participate in this program both as prostate cancer researcher and scientific reviewer. From my personal experience, I believe that the PCRCP will definitely develop a curative therapy for prostate cancer patients.”

Benyi Li, M.D., Ph.D., University of Kansas Medical Center

“Prostate cancer is a leading cause of male deaths and the PCRCP addresses this national concern. As a consumer advocate (prostate cancer survivor), the opportunity to participate in the PCRCP alongside the scientists and scholars is a magic opportunity I continue to treasure.”



Mr. Bruce Thoreson, Us TOO International, Inc.



“The words—‘You have prostate cancer.’ Words I thought I would never hear. That was twenty years ago. Then the question, what can I do to help other men never hear these words? The DoD PCRCP became part of my life when I accepted the role of a PCRCP reviewer. As a peer reviewer and a member of the PCRCP review panel, I know I am helping to find answers that will reduce the number of men hearing the words, ‘You have prostate cancer.’

I know the PCRCP has helped many men who have heard these words, and I know as the research continues, there will be fewer men hearing these words. I am honored to be a part of the DoD PCRCP team.”

Mr. Robert Carey, Georgia Prostate Cancer Coalition

“As a bladder and prostate cancer survivor, having a voice in the research aspect of my diseases gives me an opportunity to represent all of those victims in a truly meaningful manner.”



Mr. Jim Bailey, American Cancer Society



“Being a peer reviewer for the PCRCP is a wonderful opportunity to learn about the exciting and innovative ideas emerging in prostate cancer. It is also an excellent way to engage with your colleagues while serving the greater scientific community.”

***Elisabeth Heath, M.D., F.A.C.P.,
Wayne State University School of Medicine***

Biomarker Development Award

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



Daniel Lin, M.D., Fred Hutchinson Cancer Research Center (pictured left)

Jesse McKenney, M.D., Cleveland Clinic Foundation

Although prostate-specific antigen (PSA) testing, and the resulting treatment of prostate cancer is likely responsible for some of the 44% decrease in prostate cancer mortality witnessed in the United States since 1992, the detection of low-risk tumors has increased. The majority of prostate cancers currently diagnosed are low-risk tumors. There is substantial evidence that these tumors will not cause harm if left untreated. However, uncertainty remains in accurately identifying which tumors will not cause harm

to a patient. Consequently, most new cases of prostate cancer undergo radical treatment, which comes with associated effects on quality of life. This “overtreatment” of potentially indolent disease remains a major problem in this country. To reduce this overtreatment, while still diagnosing aggressive high-risk tumors early enough that they can be successfully treated, there is a critical need for molecular assays that accurately distinguish more aggressive disease from cancers that will not cause harm. Drs. Daniel Lin and Jesse McKenney, with support from a Biomarker Development Award (FY13), plan to bring such assays into clinical use for the management of patients diagnosed with early-stage prostate cancer. They are collaborating with three industrial partners to clinically validate established biomarkers for their ability to distinguish aggressive from indolent disease in men with apparently low-risk disease by standard clinical assessments. The framework for their research is the Canary Prostate Active Surveillance Study (PASS), a unique multi-institutional biorepository and cohort of men who have chosen to manage their clinically localized prostate cancer with active monitoring by clinical exams, PSA tests, and prostate biopsies; therapeutic treatment is only recommended if or when there are indications of more aggressive cancer. They are analyzing blood, urine, and tissue specimens from men enrolled in PASS and are looking for differences in biomarker levels among men whose disease has progressed compared to the levels among men with no evidence of progression. The results of this research will immediately demonstrate the utility of available molecular assays, used in combination or alone, for the management of patients with early-stage prostate cancer. The successful validation of biomarkers that can inform physicians about when to confidently recommend active surveillance or radical therapy to their patients would bring extraordinary improvement to the care of prostate cancer patients.



Development and Evaluation of a Blood-Based Biomarker Assay to Measure Response to the Prostate Cancer Therapies Enzalutamide and Abiraterone

Jun Luo, Ph.D., Johns Hopkins University (pictured)

Stephen Plymate, M.D., University of Washington

Johann de Bono, M.B., Ch.B., F.R.C.P., M.Sc., Ph.D., F.Med.Sci., Institute for Cancer Research

For men with metastatic prostate cancer that is growing despite hormonal therapy, there are two drugs that can help: enzalutamide and abiraterone. However, they are very expensive, costing as much as \$100,000 a year, and not every man responds to either drug. Until now, the only way doctors could determine which one of these drugs to use was to prescribe one and see if it worked. Drs. Jun Luo, Stephen Plymate, and Johann de Bono are collaborating, with funding from a Biomarker Development Award (FY14), to validate and implement a simple blood test that will save these men time and money, and enable their doctors to prescribe more effective therapies.

In an earlier project funded by the PCRP, Dr. Luo found that a variant form of the androgen receptor (AR), AR-V7, could be detected in circulating tumor cells of patients with castration-resistant prostate cancer, and that patients positive for AR-V7 did not benefit from enzalutamide or abiraterone treatment. These findings were significant because they suggested that AR-V7 could be used as a blood-based biomarker to predict resistance and response to enzalutamide and abiraterone. Funds from their Biomarker Development Award

Advancements in Precision Medicine by Moving Promising Biomarkers into Clinical Practice

Assessing the Clinical Utility of the Oncotype DX Test for Improving Treatment Choice among African American Men with Non-High Risk Prostate Cancer



Peter Gann, M.D., Sc.D., University of Illinois at Chicago (pictured left)

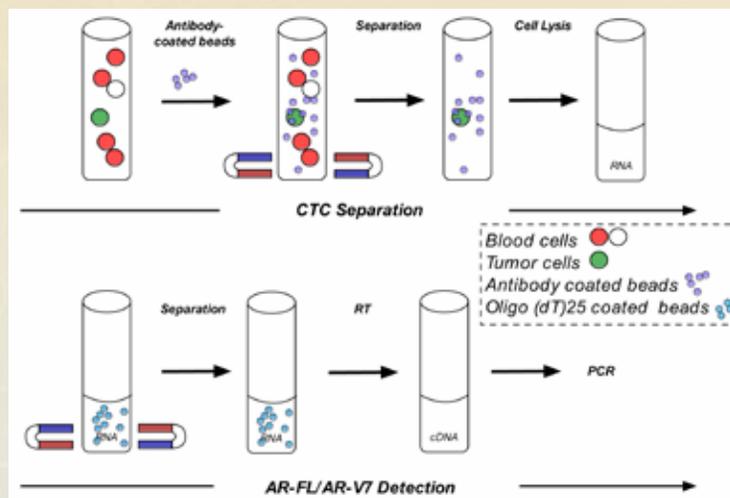
Adam Murphy, M.D., Northwestern University

Men who have just received a diagnosis of prostate cancer face a very difficult choice – whether to undergo immediate treatment with surgery or radiation, and all the risks involved – or to undergo monitoring, an approach known as “active surveillance.” A new test called the Oncotype DX Prostate Cancer Assay measures the expression level of 17 genes from prostate biopsy tissue samples, and it has undergone validation in terms of its ability to predict

aggressive prostate cancer. However, the assay’s performance in African American (AA) men has not been fully assessed, and its impact on a patient’s treatment decisions and psychological well-being remains unknown.

To address these issues, Drs. Peter Gann and Adam Murphy and their research team of highly experienced clinicians and investigators in the field of racial disparities and provider-patient communication, with support from a Biomarker Development Award (FY14), will evaluate whether the Oncotype DX test can improve outcomes for AA prostate cancer patients. They are initiating a clinical trial of 300 predominantly AA men recently diagnosed with non-high risk prostate cancer. The men will be randomly divided to receive either the standard-of-care counseling or counseling with Oncotype DX testing. The team will determine how the test affects patients’ decisions regarding treatment, as well as their psychological state surrounding the process. Additionally, they will follow the patients throughout their journey to determine how accurately the new assay predicts adverse pathology. In the end, the results from this trial will provide actionable new information that may help improve the clinical management for men, especially AA men, faced with the decision about whether or not to undergo immediate therapy for their prostate cancer.

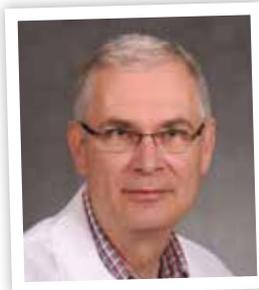
will enable Drs. Luo, Plymate, and de Bono to conduct large-scale, multi-institutional studies to further refine and validate their biomarker assay for use in clinical laboratories. Results from these studies will lead to an approved assay for use by doctors and patients that would help them determine the best course of treatment for metastatic prostate cancer. Dr. Luo also expects that this assay could be used in clinical trials for the development of new therapies designed to overcome resistance to abiraterone and enzalutamide.



Blood-based assay to detect levels of AR variant, AR-v7. After circulating tumor cells (CTCs) are captured and isolated from blood samples using an antibody specific for tumor cells, the levels of the variant AR, AR-V7, can be measured by RT-PCR.

IMPACT

Supporting research that has the potential to make a major impact in eliminating death from prostate cancer and enhancing the well-being of men experiencing the impact of the disease.



Focus Areas: Therapy

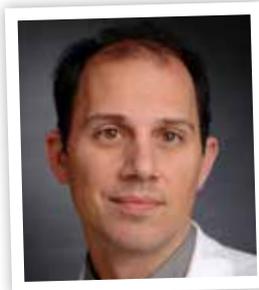
Reducing Toxicity of Radiation Treatment of Advanced Prostate Cancer

Ulrich Rodeck, M.D., Ph.D., Jefferson Medical College

Although radiation therapy has become much more refined in recent years, it remains a challenge to sufficiently dose the tumor while sparing the surrounding tissue. This is particularly relevant for radiotherapy of locally advanced prostate cancer, which is encumbered by adverse effects on the bladder and gastrointestinal (GI) systems. The only drug currently approved by the FDA for radiation protection is called amifostine; however, it has a number of side effects including severe nausea or vomiting that make it an unappealing choice for patients and clinicians.

Dr. Ulrich Rodeck and colleagues, with funding from an Idea Development Award (FY11), identified a synthetic triterpenoid (RTA 408) as a robust radiation protector of the GI tract. Interestingly, the researchers observed that when RTA 408 was given in combination with radiation to mice with prostate tumors, RTA 408 conferred radiation protection to sites that are usually most susceptible to radiation damage, including the GI tract and blood cells in the bone marrow, but it did not protect prostate cancer cells in the tumor from radiation. Rather, when used in combination with radiation, RTA 408 amplified the antitumor effect of radiation alone. Further work showed that, when given alone, RTA 408 also slowed the growth of prostate tumors in mice, underscoring its potential as an anti-cancer drug. The effects of RTA 408 are shared by other compounds (for example, parthenolide derivatives) with a similar molecular target spectrum. Understanding these mechanisms is likely to further advance drugs in this promising area.

Currently, RTA 408 is being developed by REATA Pharmaceuticals for a number of clinical applications, including ongoing clinical trials in cancer patients. Reduction of radiation-associated bladder and GI damage may translate into significant improvements in the well-being of patients undergoing radiation therapy for locally advanced prostate cancer.



Focus Areas: Biomarker Development; Tumor Microenvironment and Biology

Genetic Clonal Diversity as Biomarker for Aggressive Gleason 7 Prostate Cancer

Mark Pomerantz, M.D., Dana-Farber Cancer Institute

Gleason score, based on the pathology of prostate cancer cells, is one of the most reliable indicators of prostate cancer prognosis. However, no reliable biomarkers exist to help doctors predict the risk of aggressive cancer within a particular Gleason category. This is especially important for patients with a Gleason score of 7. Approximately 30%-40% of men diagnosed in a given year are Gleason 7, but cancer aggressiveness varies widely among these patients. Some men develop cancer that could be lethal if not treated aggressively, whereas some cancers will not cause harm if left untreated. Unfortunately, the lack of reliable biomarkers for risk means that doctors and patients take the “better safe than sorry” approach, which, for many men, means unnecessary medical expense and unpleasant, long-lasting side-effects.

Dr. Mark Pomerantz, with funding from an Idea Development Award (FY11), is developing a new biomarker to predict the aggressiveness of Gleason 7, intermediate-grade prostate cancer. Cancer cells mutate at a high frequency relative to other cells in the body, leading to many different cell types within a tumor. Some of these random mutations will provide an advantage to individual cells, allowing them to replicate more readily forming clones within the tumor. Dr. Pomerantz's project is based on the hypothesis that the more clones that form in a tumor (termed clonal diversity) the more likely it is that an aggressive clone capable of invasion and metastasis will be produced. He is analyzing prostate cancer tissue from hundreds of patient samples at the genetic and molecular level, and comparing the data to tumor pathology and patient outcome. From this data, a clonal diversity index will be developed that can be used to assess cancers at the time of diagnosis, and predict the risk for aggressive versus non-aggressive disease.

Biomarkers in the Detection of Prostate Cancer in African Americans

William E. Grizzle, MD, Ph.D., University of Alabama at Birmingham (pictured left)

Sandra M. Gaston, Ph.D., Tufts Medical Center



AA men are more likely to be diagnosed with prostate cancer than European American men, and their cancers are more likely to be aggressive as well. Unfortunately, few studies have actually evaluated the molecular differences in the prostate cancer from these two racial groups due to a lack of appropriate AA patient samples. This is because many AAs elect nonsurgical therapy for their prostate cancer (usually radiation therapy), and many present with late-stage inoperable tumors. As a result, most molecular studies, which rely on prostate cancer tissue from radical prostatectomies, do not include a sufficient number of samples of high-risk patients, especially

AA high-risk patients, to provide information that can be translated to the clinic. Use of prostate biopsy tissue would provide researchers with access to samples otherwise not available, but biopsies yield very tiny tissue samples that are needed for diagnosis, leaving little tissue for molecular research. Drs. William Grizzle and Sandra Gaston were awarded a Synergistic Idea Development Award (FY09), to use their combined expertise to analyze these high-risk cancers, particularly AA high-risk prostate cancers that are generally treated nonsurgically. They have developed an innovative “tissue print” technology that has allowed them to obtain samples from biopsies without compromising pathology diagnosis. Their analysis of these cancers has revealed prostate cancer subtypes that were either unrecognized or significantly underestimated in previous studies. These include alterations in genes that control prostate cancer lipid processing and metabolism that may reveal links between diet, obesity, and aggressive forms of prostate cancer. Ancestry genotype analysis was performed in collaboration with Dr. Rick Kittles, an expert in this area. The results showed that individuals with a high proportion of West African genetic ancestry were more likely to be diagnosed with high-grade prostate cancer on biopsy than AAs with greater than 25% admixture. This suggests that ancestry genotyping may be helpful in assessing an individual’s prostate cancer risk, and may provide useful information for AA men who are considering active surveillance over immediate treatment.

Funds from this award enabled the research team to establish the Birmingham Alabama Prostate Cancer (BAPrCa) Consortium, with a major focus on the molecular analysis of prostate biopsies to identify clinically relevant biomarkers. In addition, they are identifying ancestral markers to improve the accuracy and diagnostic power of prostate biopsy for AA patients. The collaborative team now includes urologists and radiologists who specialize in Magnetic Resonance Imaging (MRI)-guided prostate biopsy, and they are increasingly focused on incorporating this important new technology into their BAPrCa prostate biopsy studies aimed at overcoming barriers to inclusion of AA and other high-risk prostate cancer patients in molecular research studies.

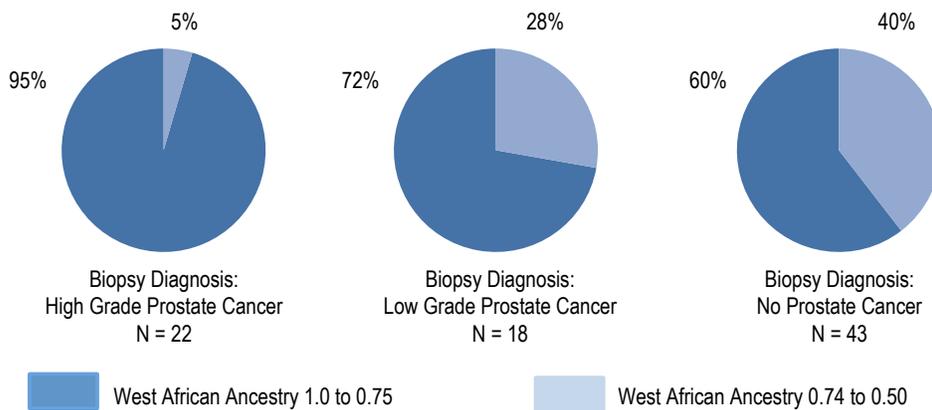


Table 1: Genotype estimates of West African Ancestry Comparing High Grade vs Low Grade vs No Cancer on Prostate Biopsy. The non-West African admixed ancestry in this study population genotyped as European in origin.

Diagnostic Group Comparison		P value
High Grade vs. No Cancer	***	P = 0.001
Low Grade vs. No Cancer	ns	P = 0.232
High Grade vs. Low Grade	ns	P = 0.035



Focus Areas: Imaging; Biomarker Development

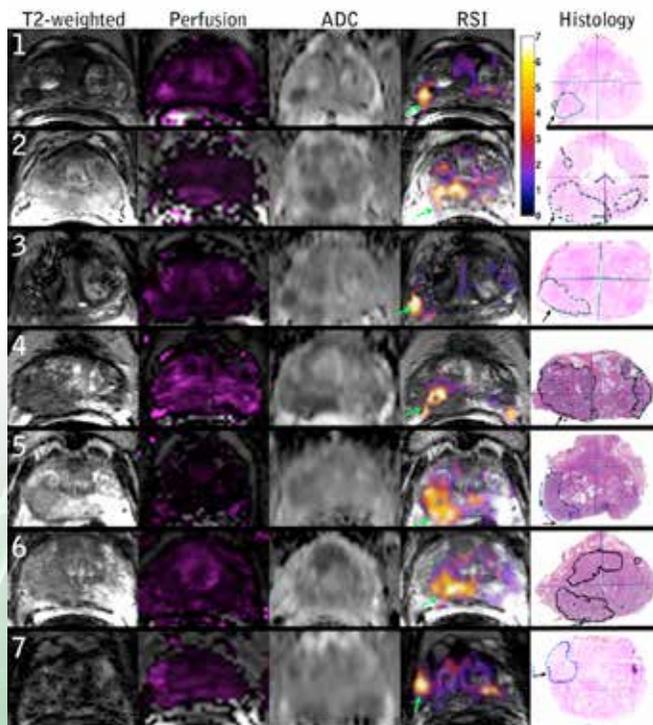
Restriction Spectrum Imaging (RSI): A Rapid, Low-Cost, Noninvasive Method for Distinguishing Indolent from Aggressive Prostate Cancer

Dr. David Karow, M.D., Ph.D., University of California, San Diego

A major focus of prostate cancer research is to develop an accurate, noninvasive method to not only detect prostate cancer, but also to determine which patients have aggressive disease that requires immediate treatment, and which have low-grade indolent tumors that can be safely monitored and perhaps forego treatment altogether.

With support from an Idea Development Award (FY12), Dr. David Karow developed a noninvasive imaging test to detect and distinguish aggressive from indolent prostate cancer, by utilizing an enhanced MRI technique called Restriction Spectrum Imaging (RSI). This technique was originally pioneered at UCSD for the detection and characterization of brain tumors. RSI measures the restricted diffusion of water within a cell, which differs between normal prostate tissue and cancerous tissue due to alterations in cell morphology. These seemingly subtle differences are measurable by MRI scanners and have been found to be highly correlated with biopsy sample analysis and Gleason grade. In addition, Dr. Karow and his team found that a rapid 5- to 10-minute exam that includes RSI is just as capable of detecting high-grade disease as a full 60-minute contrast-enhanced, multi-parametric MRI.

Dr. Karow and his team have since expanded the applications of RSI to include improved direction of targeted procedures including biopsy collection. Furthermore, working with UCSD Urology faculty, the team has brought this technique into clinical practice. RSI is now utilized on all patients imaged at the UCSD medical center, and they are actively engaged with other, select institutions to make this imaging technique more widely available as a noninvasive, rapid in vivo biomarker for prostate cancer detection and characterization.



MRI and whole mount pathology for 7 prostate cancer patients. Column 1: T2 - weighted images; column 2: Perfusion Ktrans maps; column 3: standard apparent diffusion coefficient (ADC) maps (b = 0, 100, 400, and 800 s/mm²); column 4: RSI z-score maps; column 5: whole mount pathology with tumor and area of EPE identified. Color bar represents z-scores from 0 to 7 for the RSI maps. (Rakow-Penner et al. Novel Technique for Characterizing Prostate Cancer Utilizing MRI Restriction Spectrum Imaging: Proof of Principle and Initial Clinical Experience with Extraprostatic Extension. *Prostate Cancer Prostatic Dis.* 2015 March; 18(1):81-5).



Top row from left – Mr. Clinton Burnside, Dr. Chile Ahaghotu (co-PI), Dr. Kerry Kilbridge (co-PI);
Bottom row from left – Mr. Christopher Coleman, Ms. Jamilah Brooks, Ms. Donna Durante-Lyles

Focus Areas: Health Disparity; Survivorship with Palliative Care

Improving Health Literacy in African American Prostate Cancer Patients

Kerry L. Kilbridge, M.D., M.Sc., Dana-Farber Cancer Institute

Chile Ahaghotu, M.D., Howard University

Preliminary studies have revealed health literacy barriers that interfere with the ability of many underserved AA men to understand prostate cancer treatment choices and side effects using widely available educational materials and decision aids. These obstacles include poor comprehension of common medical terms, decreased reading skills, inadequate math skills and difficulty identifying key anatomic structures needed to understand treatment choices for early stage prostate cancer. Ignoring poor health literacy denies

patients the opportunity to give informed consent and leaves prostate cancer survivors with side effects, like impotence, incontinence, or bowel symptoms, that were not of their choosing.

Devoted to addressing health disparities and improving outcomes in underserved patients, Dr. Kerry Kilbridge, in collaboration with Dr. Chile Ahaghotu, and with funding from a Health Disparity Research Award (FY12), have created a scripted, low literacy educational supplement to augment the information prostate cancer patients receive from their urologist and help them better understand their treatment options and potential side effects. The educational supplement does not rely on a patient's reading or math skills, and it allows the patient to choose between colloquial or medical terms to discuss genitourinary function and learn about treatment options. The educational supplement is currently being tested in a group of newly diagnosed AA prostate cancer patients at Howard University Cancer Center. Based on the results, Dr. Kilbridge and team will optimize the supplement and make it publically available through the National Medical Association and the American Urological Association. This project is the culmination of more than a decade of work by this team to improve survivorship and mitigate an important contributor to prostate cancer health disparities.



Focus Areas: Biomarker Development; Tumor and Microenvironment Biology

Inflammation as a Predictor of High-Grade Prostate Cancer and Recurrence after Prostatectomy

Elizabeth A. Platz, Sc.D., M.P.H., Johns Hopkins University

A large body of evidence links chronic inflammation and cancer, so what can inflammation in the prostate tell us about prostate cancer risk and prognosis? Dr. Elizabeth A. Platz, with funding from a Population-Based Research Award (FY11), is conducting a prospective evaluation of two groups of men to determine whether inflammation in the prostate can be used as a marker for risk of

future prostate cancer, and for prognosis after prostatectomy.

In one study, men without prostate cancer underwent biopsies and were then followed for a diagnosis of prostate cancer. Prostate tissue from men months to years prior to a cancer diagnosis was compared to men who did not develop prostate cancer. While the results were not significant, they did suggest that the presence of inflammation in prostate tissue may influence the development of prostate cancer. In the second study, men with clinically localized prostate cancer were treated with prostatectomy and then followed for recurrence. Prostate tissue (benign and tumor) was analyzed, both in men whose cancer recurred and in those whose did not recur, for evidence of a particular type of immune cell called the mast cell. The team found that a greater density of these immune cells in tumor tissue was associated with a lower chance of cancer recurrence. On the other hand, a greater density of these immune cells in normal prostate tissue was associated with a greater risk of recurrence. These results suggest that mast cells should be further studied for potential as a marker for prostate cancer recurrence. Dr. Platz and her team are currently searching for additional markers of inflammation that predict the risk of aggressive prostate cancer.

This award also supported the development of a publicly available resource [through SWOG] for prostate cancer researchers: prostate biopsy and clinical data from a cohort of men prior to diagnosis. This is currently the ONLY resource of its kind for prospectively testing the association of tissue markers in men without prostate cancer, and who did not have an indication for biopsy and the future incidence of cancer.



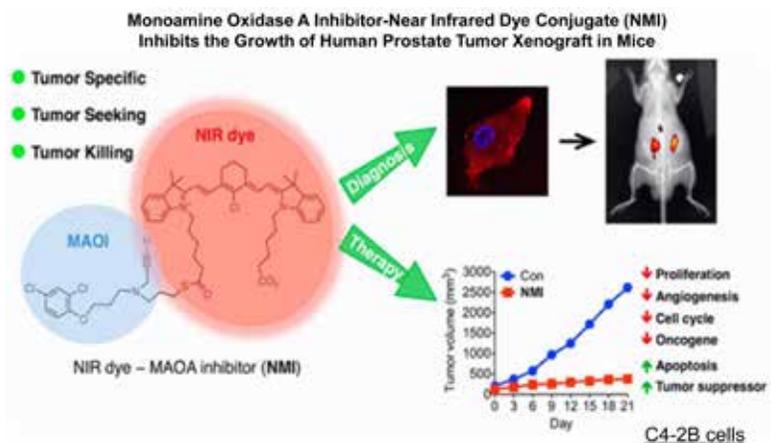
Focus Areas: Biomarker Development; Therapy; Tumor Microenvironment and Biology

MAOA Inhibitors: Using Clinical Antidepressants as Novel Therapies for Prostate Cancer

Jean Chen Shih, Ph.D., University of Southern California

Current therapies and interventions for prostate cancer have helped to extend the life of afflicted men; however, in some cases, these treatments prove to be insufficient, in particular, for advanced metastatic and castration-resistant forms of the disease. Deeper understanding of the cellular roles of specific proteins can provide insight into the mechanisms that drive prostate cancer growth and metastasis. Published data has shown monoamine oxidase A (MAO-A), a protein that regulates neurotransmitters in the brain and peripheral tissues, is highly expressed in human prostate cancer cells. This finding led the University of Southern California's Dr. Jean C. Shih, a leader in molecular neuroscience and the first to define the two types of monoamine oxidases (MAO-A and MAO-B), to investigate what role MAO-A might play in prostate cancer.

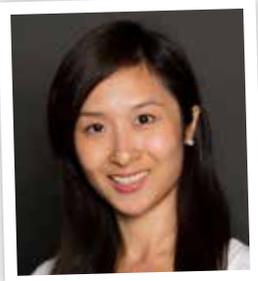
With support from an Idea Development Award (FY11), Dr. Shih set out to investigate if MAO-A was a viable therapeutic target for prostate cancer. In initial studies, Dr. Shih and her team found that prostate cancer cells without the MAO-A protein did not form tumors when implanted into animals. She discovered that, mechanistically, MAO-A supports prostate cancer growth and metastasis through free radicals and oncogenic signaling, and that an MAO-A inhibitor drug called clorgyline can slow the growth of prostate tumors in animals. Beyond these efforts, Dr. Shih and her collaborators have developed NMI, a near-infrared dye that targets cancer cells connected to the drug clorgyline. Recent experiments have shown that this dye-drug conjugate selectively targets prostate cancer cells with no accumulation in normal tissues and effectively reduces the size of tumors (tumor burden) in an animal model of prostate cancer. Overall, the team is very enthusiastic about the potential for these research findings to impact current cancer therapeutic modalities.



The tumor targeting property of NMI is shown through imaging, and inhibition of MAO-A using NMI in human prostate cancer C4-2B cells reduced tumor growth in mice.



INNOVATION Supporting novel, high-risk ideas that have the potential to make significant advancements in prostate cancer research.



Focus Areas: Therapy

Targeting GPR30 in Abiraterone- and MDV3100-Resistant Prostate Cancer

Hung-Ming Lam, Ph.D., University of Washington

Important advances in our understanding of metastatic castration-resistant prostate cancer (mCRPC) have led to the development of abiraterone and enzalutamide/MDV3100, which have been shown to increase patient survival, delay chemotherapy, and increase patient quality of life, among other benefits. However, resistance to these drugs can develop over time, making

them ineffective, so addressing mechanisms of resistance and developing new, effective strategies to overcome treatment resistance is a major concern. One key characteristic of both abiraterone and enzalutamide is that they reduce the levels of tumor androgens or androgen signaling to an ultra-low level, thus effectively suppressing tumor growth. This ultra-low level of androgen signaling may provide new directions for research into mechanisms of resistance because therapeutic targets that are expressed at high levels under ultra-low androgen conditions may be ideal candidates for drug development.

Dr. Hung-Ming Lam has shown that the expression of G protein-coupled receptor 30 (GPR30), an estrogen receptor, increases in an androgen-deprived environment and is detected at high levels in 80% of CRPC metastases. This high expression was also detected in both abiraterone- and enzalutamide-resistant prostate cancer metastases to lung and bone obtained through the rapid autopsy program at the University of Washington. She has also found that a specific agonist for GPR30, called G-1, inhibits prostate cancer growth. With funding from an Idea Development Award (FY13), Dr. Lam is conducting highly innovative preclinical studies using newly established abiraterone- and enzalutamide-resistant patient-derived cells to evaluate the efficacy and mechanism of GPR30 agonist G-1 in inhibiting tumor growth, and she will determine the role of intratumoral androgens in G-1 responsiveness and resistance. Men with abiraterone- or enzalutamide-resistant mCRPC may be profoundly affected, in the long term, by this project. It may provide the preclinical evidence to incorporate GPR30 as a routine diagnosis marker for formulating treatment options using the GPR30 agonist G-1.



Focus Areas: Therapy; Tumor Microenvironment Biology

Immunological Targeting of Tumor-Initiating Prostate Cancer Cells

Charles G. Drake, M.D., Ph.D., Johns Hopkins University

It has long been known that a small population of epithelial cells, called castrate-resistant luminal epithelial cells, is left behind in the prostate gland after androgen-deprivation therapy. More recent studies suggest that these epithelial cells might be the ones that eventually give rise to later stage, castration-resistant cancers. Dr. Charles Drake believes that elimination of these cells, at an early

stage – right after initial androgen deprivation therapy – might delay or prevent prostate cancer progression.

With funding from an Idea Development Award (FY12), Dr. Drake hopes to employ the patient's immune system – a powerful tool capable of precisely distinguishing one cell from another – to eliminate castrate-resistant luminal epithelial cells. He and his team will first identify target proteins (antigens) on castrate-resistant luminal epithelial cells. Using these proteins, they will then construct a bacteria-based vaccine; these vaccines present their target proteins (antigens) in a manner that powerfully activates the immune system.

Another unique aspect of Dr. Drake's approach is his plan to use a novel immune-activating protein (an "adjuvant") – derived from bacteria. These proteins, known as cyclic-dinucleotides, incorporate most of the power of bacterial vaccines, without their complexity. Using this adjuvant will allow Dr. Drake to generate and screen a large number of unique vaccines that target different proteins present on the castrate-resistant luminal epithelial cells. The vaccines that induce the best immune response in mice without cancer will then be tested in mice with prostate cancer to determine which are most effective. If successful, these studies will lead to clinical trials in humans and, perhaps, to a new treatment paradigm for prostate cancer that recurs after primary therapy.

Development of a New Class of Drugs to Treat Castration-Resistant Prostate Cancer

Scott Dehm, Ph.D., University of Minnesota (pictured left)

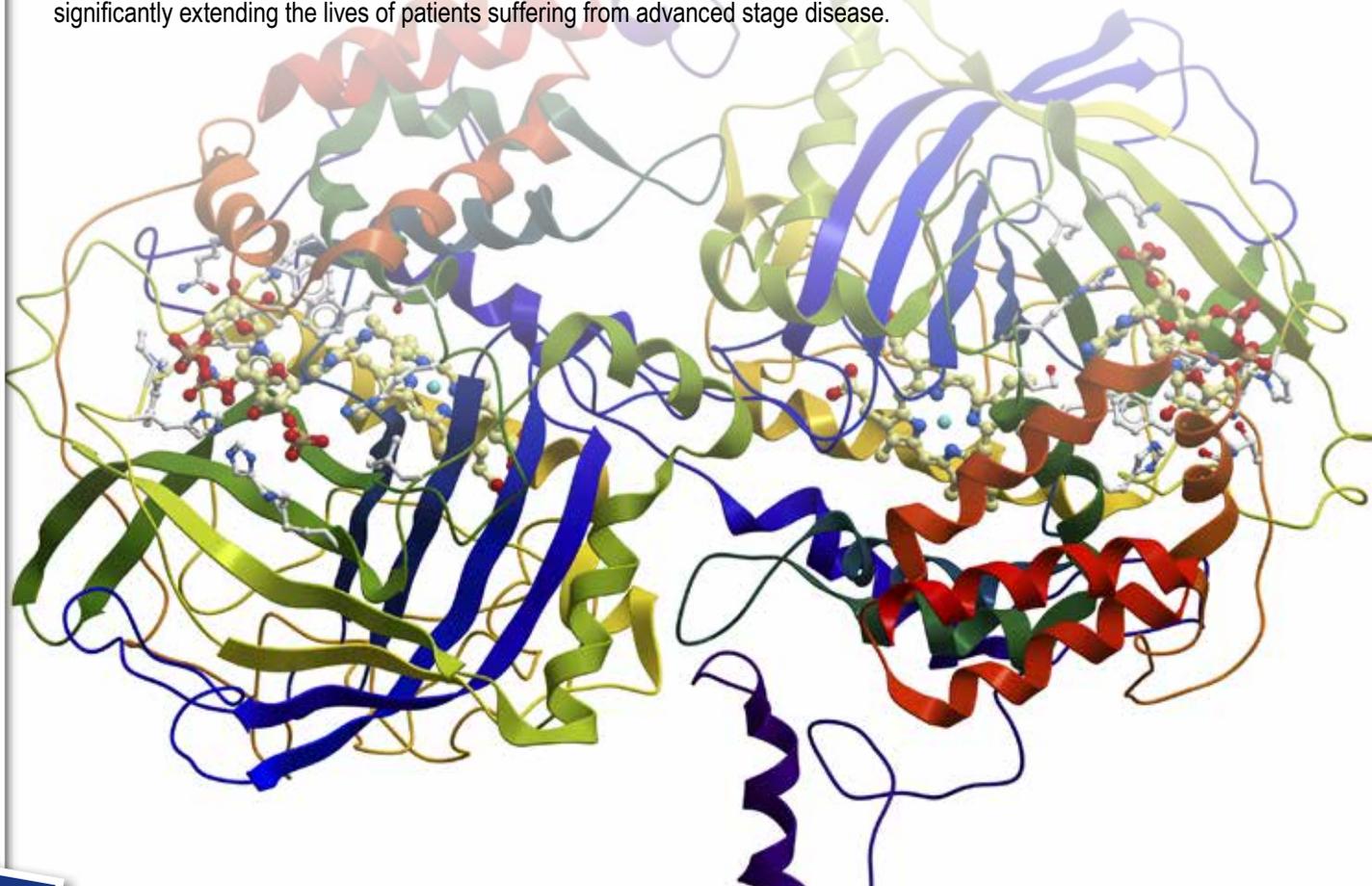
Paul Rennie, Ph.D., Vancouver Prostate Centre at the University of British Columbia (center)

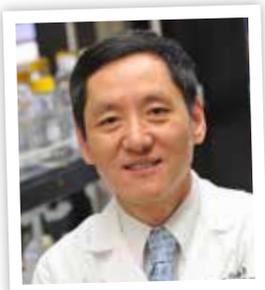
Daniel T. Gewirth, Ph.D., Hauptman-Woodward Medical Research Institute



Treatment of patients with advanced-stage prostate cancer relies on hormone-like drugs that target a single, precise region of the AR, a key protein in the disease. Treatment with these hormone-mimicking drugs is initially quite successful, usually leading to a significant remission of the disease. After a while, however, the cancer inevitably returns because the AR in the tumor changes, becoming resistant to the hormone-like drugs. The team of Drs. Dehm, Gewirth, and Rennie, with funding from

a Synergistic Idea Development Award (FY13), is developing an entirely new class of drugs that target a different region of the AR. This other region is trickier to design drugs for, but in return, it has several advantages. It changes less frequently than the hormone-targeted region, and it is more crucial for the AR to function. Drugs that can target this region of the AR thus have great potential to continue working long after a prostate cancer has become resistant to the conventional drugs. The research team, using their combined expertise in the structure and function of the AR, has discovered lead compounds of this new class of drug. Promising candidates are being tested and further refined for the highest levels of anti-cancer activity. The Rennie and Cherkasov laboratories (Vancouver Prostate Centre) are working to improve the drug candidates and determine their efficacy against tumor growth. The Dehm lab (University of Minnesota) is working to understand the effects of this treatment on gene expression in prostate cancer cells. Finally, the Gewirth lab (Hauptman-Woodward Institute) is determining the structural basis for the interaction between the drug candidates and the AR. Together, this work will serve as a foundation for a new generation of prostate cancer drugs. It will also set the stage for Phase I clinical trials of a new, improved treatment with the goal of significantly extending the lives of patients suffering from advanced stage disease.





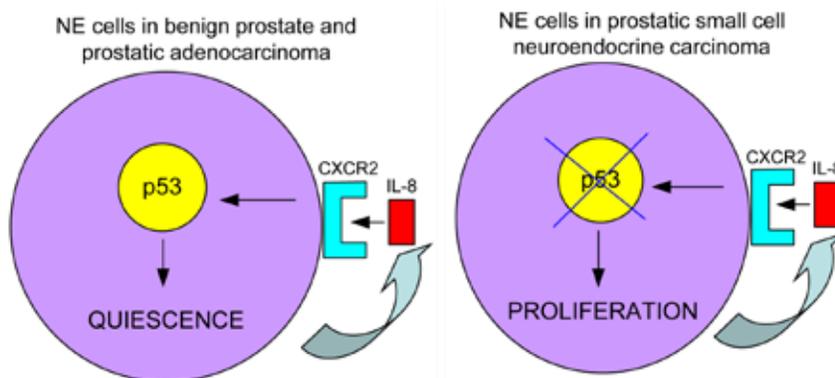
Focus Areas: Tumor and Microenvironment Biology; Therapy

The Function of Neuroendocrine Cells in Prostate Cancer

Jiaoti Huang, M.D., Ph.D., University of California, Los Angeles

Most prostate cancers are adenocarcinomas that arise from epithelial cells (basal or luminal cells) in the prostate that express AR and PSA. However, the prostate also contains another cell type, called neuroendocrine (NE) cells, that represents a relatively small component of cells in the gland that do not express AR or PSA. In addition to adenocarcinomas, prostate cancer includes a different histologic type, known as small cell neuroendocrine carcinoma (SCNC), which is extremely aggressive and rapidly fatal. SCNC occurs after hormonal therapy for adenocarcinoma at the end stage of the disease process and is observed in about 25% of metastatic cancer patients who have failed second-generation hormonal therapies.

Dr. Jiaoti Huang, a surgical pathologist, with funding from a New Investigator Award (FY06) and an Idea Development Award (FY10), studied the cell of origin and molecular basis of SCNC using cell lines and animal models. He has found that in adenocarcinomas, a signaling pathway involving the cytokine IL-8 and its receptor CXCR2 on the surface of NE cells keeps these cells from growing and proliferating. In SCNC, however, a mutation occurs in the key regulatory molecule p53, which inactivates the IL-8/CXCR2 pathway, leading to proliferation of the NE cells and development of SCNC. Dr. Huang's studies suggest that a therapeutic regimen targeting NE cells, in combination with hormonal therapy targeting the bulk, non-NE tumor cells, may have the potential to eliminate all cancer cells and cure advanced metastatic prostate cancer.



The function of IL8-CXCR2-p53 pathway in controlling the proliferation of NE cells in benign prostate, adenocarcinoma, and SCNC. The model on the left suggests that autocrine activation of CXCR2 by IL-8 activates the p53 pathway, which keeps NE cells of benign prostate and prostate cancer in a quiescent state. The model on the right suggests that p53 mutation inactivates the IL-8-CXCR2-p53 pathway, leading to rapid proliferation and aggressive biologic behavior of NE tumor cells in SCNC.



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Focus Areas: Tumor and Microenvironment Biology

Defining the Link between Obesity and the Development of Aggressive Prostate Cancer

Wilma Hofmann, Ph.D., State University of New York, Buffalo

Obesity and being overweight have been identified as risk factors for the development of specifically progressive prostate cancer. Although combined data from multiple studies have found only a slight increase in the risk of developing prostate cancer, once developed, the cancer is more likely to be aggressive in obese men than in men of healthy weight. However, little is known about

the cellular processes involved in this relationship or how diet might facilitate the occurrence of aggressive prostate cancer.

Dr. Wilma Hofmann recently traced a direct link between the presence of high levels of certain types of fatty acids in the microenvironment of cells and an increase in the metastatic potential of cells. Specifically, she found that the fat content in the cellular environment impacts the ability of cancer cells to migrate away from a primary tumor and invade other tissues. Because the presence of specific fatty acids in the microenvironment of cells is dependent on dietary intake and on other factors such as disorders that affect fatty acid/cholesterol metabolism, Dr. Hofmann, with funding from an Idea Development Award (FY13), is identifying the types and ratios of fatty acids that affect the invasive capabilities of prostate cancer cells. Her research may lead to identification of new dietary factors, metabolic conditions, and/or disorders that lead to the excess of certain fat types in the cellular microenvironment that contribute to aggressive prostate cancer.

In addition, currently, there is no biomarker available that can distinguish aggressive from indolent disease, making correct diagnosis and treatment of aggressive forms of prostate cancer difficult. This study is innovative because information resulting from this research project could potentially be used clinically to determine the risk an individual has for developing metastatic prostate cancer based on dietary behavior and/or personal metabolic processes, and to develop noninvasive diet-based options for prevention or treatment of metastatic prostate cancer.



Focus Areas: Imaging

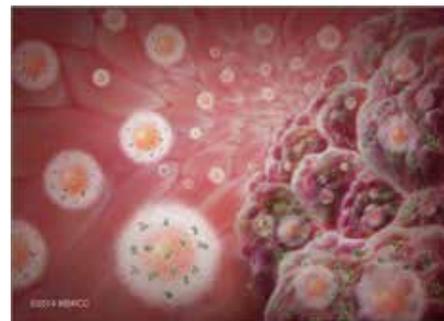
Theranostic Nanoparticles: Improved Imaging Agents Capable of Reporting on the Site-Specific Delivery of Therapeutics to Prostate Cancer Cells

Jan Grimm, M.D., Ph.D., Memorial Sloan Kettering Cancer Center

Many new therapeutics for prostate cancer never reach the clinic because they are not efficiently delivered and localized to the area targeted for treatment. Poor drug delivery and localization reduces the drug's ability to destroy the tumors, which, in turn, requires higher doses that can

increase the likelihood of adverse and toxic effects on noncancerous tissue. With support from an Idea Development Award (FY11), Dr. Jan Grimm is producing nanoparticle vehicles to improve diagnostics, and drug delivery to treat cancer.

From the outset, Dr. Grimm was investigating the use of already clinically approved nanoparticles for diagnostics by modifying these so they could specifically target an antigen on prostate cancer cells that correlates with the aggressiveness of the cancer (prostate-specific membrane antigen [PSMA]). What he found was that these particles not only specifically recognized tumor cells, but were also easily loaded with drug molecules, which makes them capable of taking drugs directly to cancer cells. With the dual functionality of both a therapeutic vehicle and diagnostic agent, these molecules are referred to as theranostic agents. A remarkable feature of the agent is that it not only helps in cancer detection but, for the first time, can be used to monitor drug release in real time using a standard MRI device. This attribute allows physicians to determine when and where drugs are being released in the patient's body during treatment. Dr. Grimm is collaborating with institutional and industrial partners to transition these agents into clinical trials that are likely to be expedited because both the nanoparticle base and the drugs are already in clinical testing or approved for clinical use.





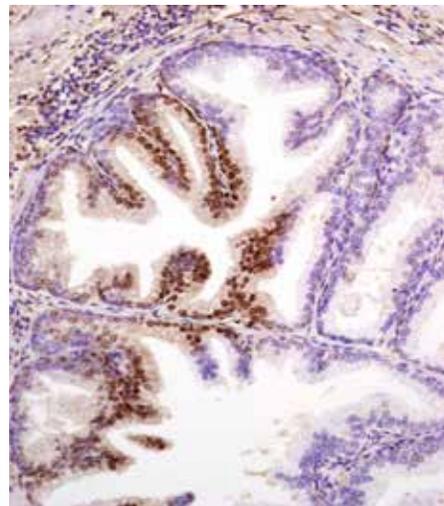
Focus Areas: Tumor and Microenvironment Biology; Biomarker Development

Runx2: A Biomarker for Invasive Prostate Cancer

Renny Franceschi, Ph.D., University of Michigan

The background of this research is a bit unusual because the primary interest of Dr. Renny Franceschi's laboratory is in the area of bone biology, not cancer. He had previously shown that a protein called Runx2 is necessary for the normal development of the skeleton, a topic he had been studying for many years. In fact, it was in bone studies that he first discovered that Runx2 was activated by phosphorylation, a specific protein modification that involves the addition of a phosphate group to the Runx2 protein. The resulting phosphorylated Runx2 (P-Runx2) is much more active than the non-phosphorylated form during bone formation. Interestingly, in addition to its role in bone formation, Runx2 is also expressed in prostate cancer cells. Dr. Franceschi proposed the intriguing idea that Runx2's role in bone formation might also be active in prostate cancer cells, and might explain the propensity of prostate cancer cells to metastasize to and grow in bone.

With support from an Idea Development Award (FY10), Dr. Franceschi assembled a team of prostate cancer investigators to study the role of P-Runx2 in prostate cancer metastasis. Using a newly created antibody that uniquely detects only the P-Runx2 protein, he screened prostate tissues from more than 100 patients. Strong P-Runx2 staining was detected in all prostate cancer samples including prostate intraepithelial neoplasia with little or no staining in normal prostate, prostatitis, or benign prostatic hyperplasia, indicating that this antibody was very good at discriminating between benign prostate diseases and cancer. Moreover, the strongest staining was with the most aggressive (high Gleason score) metastatic cancers, suggesting it may help to distinguish indolent from lethal cancer. Another notable aspect of his work is the demonstration that prevention of Runx2 phosphorylation slows prostate tumor growth. Overall, Dr. Franceschi's work has identified a new biomarker for prostate cancer that has the potential to discriminate between benign prostate disorders, less invasive cancers, and metastatic cancers, as well as provide a potential new target for drug development.



Tissue section of early prostate cancer (prostate intraepithelial neoplasia) showing P-Runx2 stained cancer cells (brown) and normal tissue (blue)

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Focus Areas: Mechanisms of Resistance and Response; Therapy

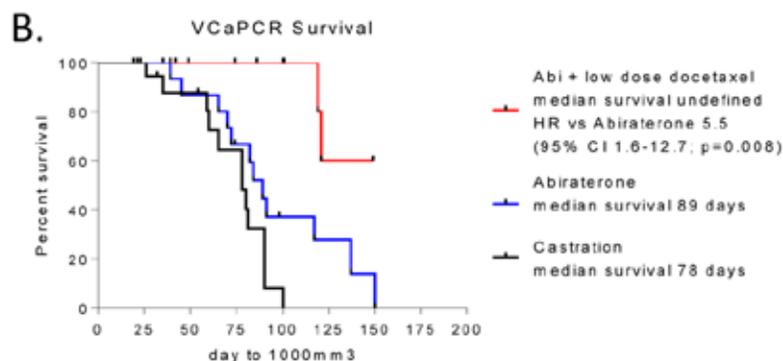
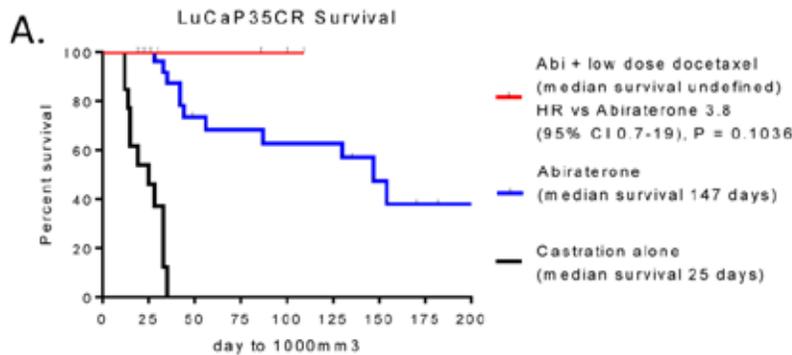
Synergism of Docetaxel with Androgen Ablation Therapy in Prostate Cancer

Elahe Mostaghel, M.D., Fred Hutchinson Cancer Research Center

Many cases of prostate cancer progress to a more advanced stage that is resistant to current therapies, and is ultimately lethal. Docetaxel chemotherapy has been one of the few life-prolonging treatment options for these men, but FDA approval of two new androgen-inhibiting drugs, abiraterone and enzalutamide, has provided these patients with new treatment options. However, the optimal combination, sequence, and timing of these drugs with docetaxel therapy have not been established.

A team of researchers led by Dr. Elahe Mostaghel received funding under the Exploration–Hypothesis Development Award mechanism to explore the innovative, untested hypothesis that these new, more effective hormone therapy agents would synergize with and enhance cancer sensitivity to docetaxel. This is particularly interesting because docetaxel has been found to also inhibit androgen activity. The team evaluated the impact of docetaxel and abiraterone on tumor growth of human-derived, advanced-stage prostate cancer in mouse models. Dr. Mostaghel found no evidence that pre-treatment of the mice with abiraterone, to suppress intra-tumor androgen activity, had any beneficial impact on sensitizing tumors to taxane therapy. Instead, their data suggested that treatment with abiraterone might decrease sensitivity to subsequent taxane therapy. This is consistent with early clinical reports showing that, following abiraterone treatment, men are essentially resistant to taxane-based chemotherapy. However, they also made the surprising discovery that a combination of abiraterone treatment with several cycles of low-dose docetaxel (which, by itself, did not have significant anti-tumor activity) actually improved treatment efficacy over abiraterone therapy alone.

To clinically validate this treatment strategy would represent an attractive compromise for patients whose disease does not yet require chemotherapy, or who are unwilling or unable to undergo full-dose taxane chemotherapy. With funding from two new FY14 PCRP awards, Dr. Mostaghel will be investigating other potential mechanisms of hormone therapy resistance, and identifying other factors and pathways that could be used to sensitize prostate tumor cells to high-dose androgen therapy.



The impact of treatment with abiraterone alone or with low-dose docetaxel on growth of castration-resistant prostate cancer xenografts. A) Kaplan Meier survival curves for LuCaP35CR tumor growth. B) Kaplan Meier survival curves for VCaPCR tumor growth.



Focus Areas: Tumor and Microenvironment Biology

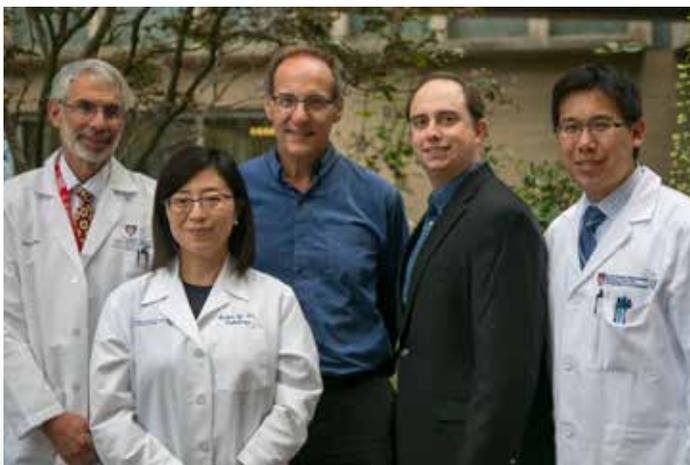
Molecular Features Distinguishing Gleason Grade 3 and Grade 4 Prostate Cancers

Adam Sowalsky, Ph.D., National Cancer Institute

A large number of men who undergo a biopsy to test for prostate cancer are found to have a nonaggressive (indolent) form of the disease based on the Gleason score that describes the pathology of the biopsy on the microscope slide. The most common Gleason pattern is 3, which lends itself to the most favorable prognosis, whereas Gleason pattern 4 has a much less favorable prognosis. The Gleason scoring system does not include any molecular or genetic criteria that might assist in determining whether a cancer is indolent (G3) or aggressive (G4) prior to surgery, or whether a cancer will progress from low-grade to high-grade cancer. Dr. Adam Sowalsky, with funding from a Postdoctoral Training Award (FY12) and under the mentorship of Dr. Steven Balk at Beth Israel Deaconess Medical Center, proposed to identify molecular features that distinguish higher-risk cancers from those that will remain indolent.

Dr. Sowalsky performed a microdissection technique that isolates ultrapure populations of cancer cells from prostate tissue, and he repeated this technique thousands of times on cancer samples from the same patient, knowing which groups of cells came from high-grade (G4) or low-grade (G3) tumor tissue. Comparing the high-grade to the low-grade cancer cells, he discovered recurring themes that may be important in understanding how an aggressive prostate cancer emerges from a low-grade cancer, including the activation of the Myc oncogene and increasing metabolic processes involving oxidative phosphorylation.

Dr. Sowalsky has accepted a tenure track position at the National Cancer Institute and has been awarded two new PCRP awards. With this new PCRP funding, he is investigating the DNA from prostate cancer cells circulating in the blood of patients to identify biomarkers that could eventually be used by clinicians to complement PSA and Gleason scores to identify aggressive disease. This research has the potential to improve the prognosis and quality of life for men recently diagnosed with prostate cancer by preventing unnecessary surgeries in those that have an indolent cancer, and identifying those men whose cancer is potentially aggressive and who need immediate treatment.



From left to right: Glenn Buble, M.D., Huihui Ye, M.D., Steven Balk, M.D., Ph.D., Adam Sowalsky, Ph.D., and Peter Chang, M.D.



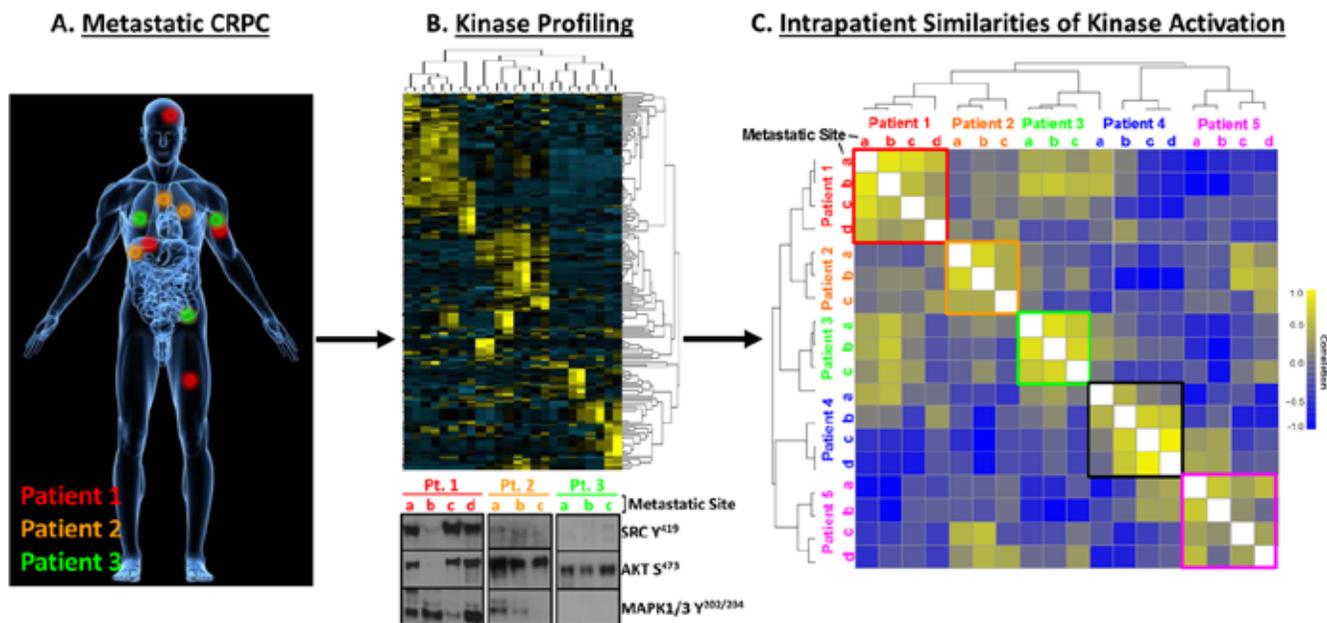
Identification and Targeting of Tyrosine Kinase Activity in Prostate Cancer Initiation, Progression, and Metastasis

Justin Drake, Ph.D, University of California at Los Angeles

Many factors contribute to the continued growth of prostate cancer cells and their resistance to treatment. Work from the laboratory of Dr. Owen Witte previously revealed mutated tyrosine kinase genes in other cancers that led to the development of kinase-targeting therapeutics, which have had a dramatic impact on patient survival in other diseases. However, these mutations are rare in prostate cancer. With support from a Postdoctoral Prostate Cancer Training Award (FY10), and under the mentorship of Dr. Witte, Dr. Justin Drake set out to identify and characterize non-mutated pathway-activated tyrosine kinases in prostate cancer to elucidate new kinase-targeting strategies for treating advanced disease.

In collaboration with the University of Michigan Rapid Autopsy Program and Dr. Thomas Graeber, a phosphoproteomic expert at UCLA, Dr. Drake discovered that metastases at different sites in the same patient expressed similar kinase activation patterns. This supports the notion that a single biopsy may be sufficient to evaluate new treatment options in patients resistant to current therapies. Next, Dr. Drake, soon to be an Assistant Professor at the Rutgers Cancer Institute of New Jersey, and Dr. Witte plan to validate their findings by evaluating these activated kinases in mouse models of human prostate cancer to determine if they are good candidates for therapeutic targets.

Drs. Drake and Witte envision this research leading eventually to clinical trials to evaluate select kinase activation states in patients with resistant tumors, which would contribute to an understanding of which patients are most likely to respond to kinase therapies and to the development of new combination therapies. Since some kinase inhibitors are already FDA-approved for treatment of other cancers, this could be quickly realized for prostate cancer patients diagnosed with castration-resistant or metastatic tumors.



Phosphoproteomic profiling and subsequent validation of kinase activation signatures reveals inpatient similarities of metastatic castration resistant prostate cancer tissues. A. Representative locations of metastatic CRPC lesions extracted for phosphoproteomic analysis. B. Phosphotyrosine peptide enrichment coupled to label free quantitative mass spectrometry and subsequent western blot data identified patterns of kinase activation. C. Pairwise Pearson correlation coefficients grouped the metastatic lesions from each patient together. Yellow shows a high degree of correlation; blue is low.



Focus Areas: Genetics; Mechanisms of Resistance and Response; Biomarker Development

Leveraging RB Status to Define Therapy for Castration-Resistant Prostate Cancer

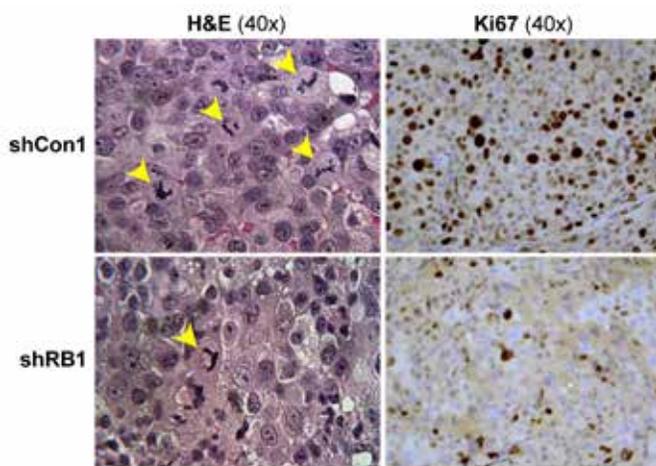
Renée de Leeuw, Ph.D., Thomas Jefferson University

In 2010, the FDA approved the next-generation taxane-based chemotherapy, cabazitaxel (Jevtana®). It shows efficacy in patients with metastatic castration-resistant prostate cancer (CRPC) whose cancer no longer responds to androgen deprivation therapy (ADT) or docetaxel, the previous generation taxane-based chemotherapy. Under the mentorship of Dr. Karen Knudsen, and with funding from a Postdoctoral Training Award (FY12), Dr. Renée de Leeuw

explored how cabazitaxel works.

In prostate cancer patients who develop resistance to ADT, many (about 60% of cases) lose a protein called the retinoblastoma tumor suppressor protein (RB). To study the possible role of RB loss in response to cabazitaxel treatment, Dr. de Leeuw took prostate cancer cells that have progressed to ADT resistance via the loss of the RB protein and injected these or RB-positive prostate cancer cells into mice. Once the tumors had formed, the mice were treated with ADT. A week later, the mice began treatment with cabazitaxel. Remarkably, Dr. de Leeuw found that after 2-3 weeks of cabazitaxel treatment, RB-negative tumors stopped growing, whereas RB-positive tumors kept growing. These data demonstrate that RB-deficient tumors are hypersensitive to cabazitaxel treatment.

These results provided the rationale behind several new multicenter Phase II clinical trials using RB as a biomarker for identifying patients who are likely to respond to cabazitaxel treatment and those not likely to respond. This could be a significant step toward precision medicine for prostate cancer patients. Dr. de Leeuw concludes that “this training award has given me the unique opportunity to see my project advance from bench to bedside, interact with cancer experts with different backgrounds, and provided me with better insight into what it takes to make laboratory ideas come to fruition, and ultimately improve treatment for cancer patients.”



Tumors that progress to CRPC by RB loss display hypersensitivity to cabazitaxel, shown by a reduction in mitotic figures and Ki67 staining after cabazitaxel in vivo.



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Focus Areas: Tumor and Microenvironment Biology; Genetics

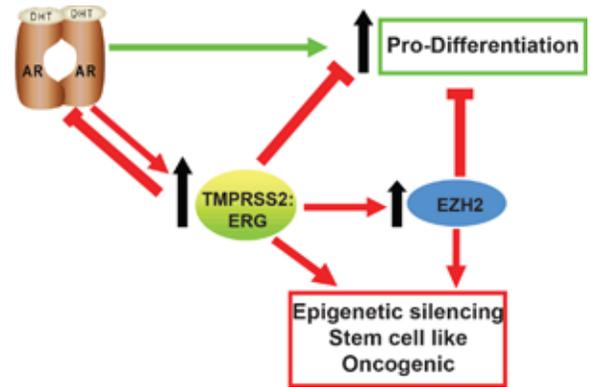
Delimiting the Regulatory Network of Master Transcription Factors in Prostate Cancer

Jindan Yu, M.D., Ph.D., Northwestern University

Understanding the molecular mechanisms of prostate cancer progression at the systems level is essential to identifying key disease pathways for therapeutic intervention and precision medicine. While at the University of Michigan, Dr. Jindan Yu, with funding from a Postdoctoral Training Award (FY06) and under the mentorship of Dr. Arul Chinnaiyan, used state-of-the-art genomics approaches and their integration in computer models to identify key molecules/pathways underlying prostate cancer progression. Dr. Yu demonstrated that a protein called EZH2 turns off the expression of a specific set of genes that block prostate cancer growth.

After completing her postdoctoral training, Dr. Yu joined the faculty at Northwestern University as an Assistant Professor. She received a New Investigator Award (FY08) to further research the molecular mechanisms by which key oncogenes EZH2 and TMPRSS2:ERG gene fusions drive prostate cancer progression.

She found that the ERG protein binds to the AR and a majority of AR target genes disrupting androgen signaling, and that ERG activates the epigenetic EZH2 pathway facilitating prostate cancer growth and cancer stem-cell-like characteristics. Dr. Yu has since received an Exploration-Hypothesis Development Award (FY12) to investigate the role RNA methylation plays in prostate cancer, and an Idea Development Award (FY12) in collaboration with Dr. Chuan He (University of Chicago). Together, they are performing genome-wide DNA methylation and hydroxymethylation profiling of prostate cancer, with the ultimate goal of developing unique and highly sensitive methylation assays for diagnosis and/or prognosis using biopsy tissues, patient serum, or urine.



Focus Areas: Therapy

Activating the Innate Immune System to Eradicate Prostate Cancer

Akash Patnaik, M.D., Ph.D., M.M.Sc., Beth Israel Deaconess Medical Center and Harvard Medical School, Boston

Several drugs targeting deregulated signaling pathways in tumor cells have been deployed in cancer therapy; however, their impact on immune responses within the tumor microenvironment is poorly understood. In particular, cabozantinib (a multi-tyrosine kinase inhibitor) elicited anti-cancer responses in clinical trials across several malignancies, including kidney cancer, medullary thyroid cancer, and CRPC with multi-organ metastases. However, cabozantinib's underlying mechanism of action across this spectrum of anti-cancer clinical responses remains unclear. Dr. Akash Patnaik is a physician-scientist with a lifelong commitment to prostate cancer research and patient care. Working with a multidisciplinary team of prostate cancer experts spanning the spectrum of basic and translational research, and with funding from a Physician Research Training Award (FY10), he explored cabozantinib's anti-cancer mechanism.

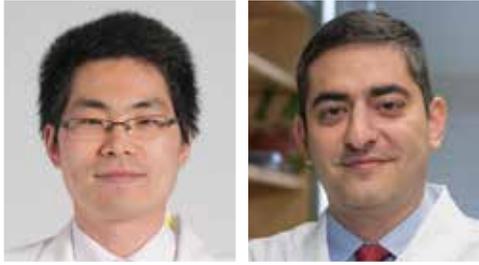
While the field of cancer immunotherapy has focused on activating T cells (adaptive immunity) against cancer, Dr. Patnaik discovered that cabozantinib triggers the activation of a different kind of immune cell called neutrophil (innate immunity) through enhanced release of neutrophil chemoattractant factors from prostate cancer cells, resulting in robust neutrophil trafficking and rapid eradication of invasive cancer in an aggressive, treatment-refractory mouse model of prostate cancer. Cabozantinib-induced tumor clearance in mice was abolished by antibodies that either deplete neutrophils or block neutrophil trafficking to the site of the cancer, demonstrating that neutrophils are responsible for this dramatic anti-cancer immune response. This is the first demonstration of a kinase inhibitor that activates innate immunity to eradicate cancer.

Based on this mechanistic insight that cabozantinib drives a neutrophil-based early, innate immune response, Dr. Patnaik and his "wonderful team of investigators" are working on the development of Phase I clinical trials that combine cabozantinib with other immunotherapies to enhance immune responses against metastatic prostate cancer.

Potential New Therapeutic for Castration-Resistant Prostate Cancer

Zhenfei Li, Ph.D., Cleveland Clinic Foundation (pictured left)

Nima Sharifi, M.D., Cleveland Clinic Foundation



Advanced prostate cancer is initially treated with ADT to block the action of male hormones (i.e., androgens), which fuel prostate cancer. While ADT is initially very effective, tumors eventually mutate allowing them to make their own supply of androgens, a disease state termed CRPC. Understanding how tumors become resistant to ADT is critical to developing newer, more effective treatments for prostate cancer.

Dr. Nima Sharifi, with funding from a Physician Research Training Award (FY08), discovered the major pathway for androgen production that drives CRPC. Furthermore, he found that in some cases of CRPC, a mutation

occurs in one of the enzymes in this pathway, 3beta-hydroxysteroid dehydrogenase (3betaHSD), which leads to increased androgen production. Patients with this mutation have profoundly worse outcomes. Dr. Zhenfei Li, under the mentorship of Dr. Sharifi, received funding from a Postdoctoral Training Award (FY12) to investigate the role 3betaHSD plays in resistance to abiraterone, an FDA-approved drug for the treatment of advanced prostate cancer that blocks androgens. Knowing the chemical structure of abiraterone, and that it is metabolized by 3betaHSD, Dr. Li hypothesized that a metabolite of abiraterone would be able to function similarly but may be more effective at inhibiting androgens. Indeed, Dr. Li identified an entirely new metabolite of abiraterone, D4A, which is present in the blood of patients who received abiraterone treatment, and blocked more enzymes in the androgen production pathway than abiraterone. These results suggest that D4A could be more effective in the treatment of prostate cancer than abiraterone itself. Drs. Sharifi and Li are currently working to determine if D4A could serve as a biomarker for clinical response or resistance to abiraterone.

Focus Areas: Therapy



Promotion of Antitumor Immune Responses with Epigenetic Modifying Agents

Joshua Lang, M.D., M.S., University of Wisconsin, Madison

With a background in molecular biology, and with a clear commitment to becoming a physician-scientist focusing on prostate cancer, Dr. Joshua Lang joined the internal medicine/medical oncology research track at the University of Wisconsin Carbone Cancer Center (UWCCC). With the support of his mentors, Dr. Douglas McNeel and Dr. David Beebe, and with funding support from a Physician Research Training Award (FY11), Dr. Lang now runs his own independent

laboratory as an Assistant Professor of Medicine at the UWCCC, and is principal investigator on multiple clinical trials at the UWCCC, as well as the co-investigator of UWCCC's clinical research site within the Prostate Cancer Clinical Trials Consortium.

During the course of this award, Dr. Lang has made great strides in understanding how prostate cancer evades the immune system, rendering current immunotherapies ineffective. He has identified a class of drugs – epigenetic modifying agents (EMAs) – that alter histone acetylation and DNA methylation, and appear to enhance antitumor immune responses and improve patient immune responses when used in conjunction with immunotherapies. However, achieving maximal antitumor effect of the combined EMAs and tumor vaccines in patients requires development of precision-dosing strategies. Thus, new biomarkers are needed to assess the impact of EMAs on the effectiveness of the vaccine therapy and to identify those patients who are receiving the most benefit. Circulating tumor cells represent one source of tumor cells that could provide a better means of doing both, and so with funding from a Synergistic Idea Development Award (FY14), Dr. Lang and Dr. Dehm of the University of Minnesota are developing biomarkers based on circulating tumor cells that can be isolated from patient blood.

Dr. Lang hopes the benefits of immune-based therapies currently used in other cancers can be extended to patients with prostate cancer. He is currently designing clinical trials for men with prostate cancer using these new epigenetics-targeting drugs and the circulating tumor biomarkers developed in his laboratory.

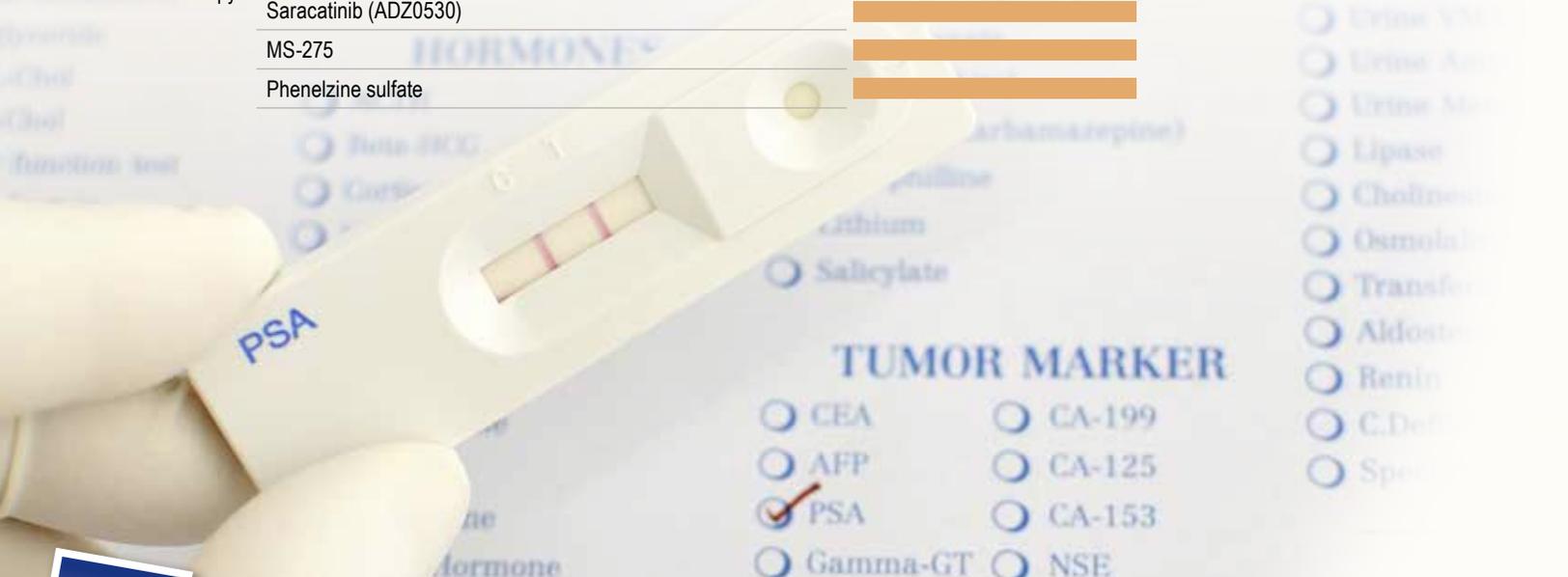
Clinical Pipeline

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 28-31.

Focus Area	Agent/Technique	Pre-Clinical	Phase I/II	Phase III	To Patients
Mechanisms of Resistance and Response	N-Cadherin signaling pathway	████████████████████			

Focus Area	Agent/Technique	Pre-Clinical	Phase I/II	Phase III	To Patients
Imaging	Multiadaptive Plan (MAP) intensity modulated radiation therapy (IMRT)	████████████████████			
	T2-weighted prostate 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	████████████████████			
	Erbium: YAG laser	████████████████████			
	124I-anti-PSCA A11 minibody	██			
	PMSA-Based positron emission tomography (PET) Imaging Agent	██			
	MRI-guided robotic device for real-time needle placement in prostate biopsy sample retrieval	██			
	Fluorine-18 Fluorocholine (FCH) PET	██			
	MRI-Based Treatment Planning for Radiotherapy	██			
Elekta Synergy	██				

Focus Area	Agent/Technique	Pre-Clinical	Phase I/II	Phase III	To Patients
Chemotherapy	SRI-28731	████████████████████			
	Gamitrinib	████████████████████			
	Berberine	████████████████████			
	Saracatinib (ADZ0530)	██			
	MS-275	██			
	Phenelzine sulfate	██			



Focus Area	Agent/Technique	Pre-Clinical	Phase I/II	Phase III	To Patients
Combination Therapy	ABT888 plus radiation				
Focus Area	Agent/Technique	Pre-Clinical	Phase I/II	Phase III	To Patients
Hormonal Therapy	Mifepristone plus enzalutamide				
	N-terminal domain inhibitor (EPI-506)				
	APC-100				
	3,3'-diindolylmethane (DIM)				
	ZYTIGA® (abiraterone acetate)				
	Xtandi® (enzalutamide)				
	Focus Area	Agent/Technique	Pre-Clinical	Phase I/II	Phase III
Immunotherapy	Lm-PCaVx (ADU-741)				
	PSA 146-154 peptide vaccine				
	BP-GMAX-CD1				
	DNA vaccine encoding PAP (pTVG-HP)				
	MEDI6383 (OX40 antibody)				
	Ipilimumab				
	Focus Area	Agent/Technique	Pre-Clinical	Phase I/II	Phase III
Radiotherapy	Intensity Modulated Radiation Therapy (IMRT)				
	¹⁷⁷ Lu-J591				
Focus Area	Agent/Technique	Pre-Clinical	Phase I/II	Phase III	To Patients
Targeted Therapy	J591- Duocarmicin conjugate				
	STA-9584				
	C-209				
	Cixutumumab (IMC-A12)				
	G-202				
	Custirsen (OGX-011)				
	XGEVA® (denosumab)				
	Velcade® (PS-341)				

Clinical Pipeline

Clinical Phase	Focus Area	Agent/Technique	PI/Mechanism	Description
Pre-Clinical	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.
Pre-Clinical	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.
Pre-Clinical	Imaging	T2-weighted prostate MRI at 7 Tesla (T) using a simplified external transmit receive coil array	Andrew Rosenkrantz Exploration Hypothesis Development Award	This study leverages the new 7T MRI scanner at New York University, which produces a magnetic field more than twice the strength of scanners currently found in the clinic. The team has designed new hardware and software to take advantage of this ultra-high field scanner, which they have now tested on two prostate cancer patients. The improvement to image quality is substantial. Testing and optimization are ongoing, as the investigators work to further harness the capabilities of a 7T MRI system and improve patient care.
Pre-Clinical	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. Pre-clinical 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.
Pre-Clinical	Imaging	Electrical Impedance Spectroscopy (EIS) for noninvasive detection of prostate tumors	Ryan Halter Prostate Cancer Training 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.
Pre-Clinical	Imaging	Erbium:YAG laser	Nathaniel Fried New Investigator Award Idea Development Award	A laparoscopic, laser imaging system utilizing two new optical techniques was developed to improve a surgeon’s ability to identify, image, and preserve the cavernous nerves during prostate cancer surgery. This system could significantly aid a surgeon’s ability to preserve sexual function after surgery, leading to improved quality of life for patients.
Pre-Clinical	Therapy (Chemotherapy)	SRI-28731	Ling Jong Idea Development Award Laboratory Clinical Transition Award	A novel dietary indole-3-carbinol, with potent activity against prostate cancer, was developed, and preclinical testing for IND submission is underway. The results so far indicate that this drug can be taken orally, is highly selective, well tolerated, and more potent than Docetaxel, the first-line treatment for metastatic CRPC.
Pre-Clinical	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. Investigational New Drug (IND) submission is underway to allow clinical testing in patients with advanced, castrate-resistant, and metastatic prostate cancer.

Clinical Phase	Focus Area	Agent/ Technique	PI/Mechanism	Description
Pre-Clinical	Therapy (Chemotherapy)	Berberine	Haitao Zhang Idea Development Award	Naturally found compound used in Chinese herbal medicine that shuts down two key cancer-promoting pathways in prostate cancer: the androgen receptor (AR) pathway and the PI3K/AKT pathway. It was also shown to reduce truncated AR-V7 splice variants, suggesting this drug could sensitize prostate cancer to existing treatments such as abiraterone, enzalutamide, and docetaxel.
Pre-Clinical	Therapy (Combination Therapy)	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.
Pre-Clinical	Therapy (Immunotherapy)	Lm-PCaVx (ADU-741)	Dirk Brockstedt Laboratory Clinical Transition Award	Vaccine designed to stimulate an immune response to three prostate cancer antigens. A Phase I clinical trial is expected to begin in 2016 in men with metastatic prostate cancer that is progressing despite ADT.
Pre-Clinical	Therapy (Radiotherapy)	Intensity modulated radiation therapy (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.
Pre-Clinical	Therapy (Targeted Therapy)	J591- duocarmicin conjugate	Neil Bander Laboratory Clinical Transition Award	This therapeutic was developed by linking J591, an antibody to PMSA, to duocarmicin, 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.
Pre-Clinical	Therapy (Targeted Therapy)	STA-9584	Andrew Sonderfan Transition Award	A novel vascular disrupting agent (VDA) that targets both new and existing prostate cancer tumors, disrupting the blood supply both in the center and at the periphery of the tumor leading to cell death. This agent has shown superior performance compared to current VDAs.
Pre-Clinical	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.
Phase I/II	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.
Phase I/II	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 and more aggressive disease. This imaging agent is in Phase I/II clinical trials to evaluate its utility in detecting advanced prostate cancer.
Phase I/II	Imaging	MRI-guided robotic device for real-time needle placement in prostate biopsy sample retrieval	Gregory Fischer Prostate Cancer Training Award New Investigator Award	MRI-guided robotic device 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.
Phase I/II	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. It is currently being tested in Phase I and II clinical trials.
Phase I/II	Therapy (Chemotherapy)	Saracatinib (ADZ0530)	Christopher Evans Idea Development Award	Non-receptor tyrosine kinase inhibitor shown to inhibit metastasis of prostate cancer with a neuroendocrine phenotype in mouse models, and preclinical results indicate it holds promise as a combination therapy. This drug has progressed to Phase I/II clinical trials.

Clinical Phase	Focus Area	Agent/ Technique	PI/Mechanism	Description
Phase I/II	Therapy (Chemotherapy)	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, combination of entinostat with CRA 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).
Phase I/II	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, the agent is currently being tested in a Phase II clinical trial on non-metastatic, recurrent prostate cancer.
Phase I/II	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 GR blocker, in addition to enzalutamide, an AR blocker, to determine if this combination treatment can overcome ADT resistance in patients with CRPC.
Phase I/II	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 AR N-terminal domain and can block transcriptional activities of truncated splice variants of AR. Unlike other hormonal therapies, this drug's mode of action may be able to overcome CRPC. EPI-506 is entering Phase I/II clinical trials for the treatment of patients with CRPC.
Phase I/II	Therapy (Hormonal Therapy)	APC-100	George Wilding Idea Development Award	A small molecule inhibitor of the AR derived from vitamin E, was shown to inhibit the growth of both androgen-dependent and -independent prostate cancer, delay tumor progression, and increase survival in pre-clinical studies. APC-100 is now in a Phase I/II clinical trial in men with advanced prostate cancer.
Phase I/II	Therapy (Hormonal Therapy)	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 and slow the growth of prostate cancer cells. DIM has progressed to Phase I and II clinical trials.
Phase I/II	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.
Phase I/II	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. A Phase I/II trial in patients with advanced, androgen-independent prostate cancer has been completed.
Phase I/II	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 a Phase II clinical trial in men with non-metastatic prostate cancer to inhibit prostate cancer recurrence.
Phase I/II	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. It is currently being tested in a Phase I clinical trial in partnership with MedImmune.

Clinical Phase	Focus Area	Agent/ Technique	PI/Mechanism	Description
Phase I/II	Therapy (Radiotherapy)	177Lu-J591	Scott Tagawa and Neil Bander Idea Development Award Phase II Idea Development Award Clinical Trial 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 PCRP.
Phase I/II	Therapy (Targeted Therapy)	Cixutumumab	Stephen Plymate Idea Development Award	A monoclonal antibody that targets insulin-like growth factor 1 receptor was shown to be effective as a single agent in prostate cancer. A recent study concluded that Cixutumumab plus AD did not significantly increase the undetectable PSA rate in men with new metastatic hormone-sensitive prostate cancer.
Phase I/II	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 is underway in patients with localized, high-risk prostate cancer prior to prostatectomy.
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 is in a Phase III clinical trial in men with metastatic prostate cancer who have not received chemotherapy.
Phase III	Therapy (Targeted Therapy)	Custirsen (OGX-011)	Kim Chi Clinical Trial Award	A second generation antisense molecule that blocks the cytoprotective protein clusterin, thereby sensitizing prostate cancer cells to chemotherapy. Custirsen in combination with chemotherapy is now in Phase III trials in men with metastatic CRPC.
To Patients	Imaging	MRI-Based Treatment Planning for Radiotherapy	Lili Chen New Investigator Award Idea Development Award	A magnetic resonance imaging (MRI)-based treatment planning protocol for 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.
To Patients	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, with over 80% of radiation machines sold today being equipped with it.
To 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 Prostate Cancer Clinical Trials Consortium.
To Patients	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.
To Patients	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.
To Patients	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.

Research Resources: Supporting

Under the guidance of leading prostate cancer scientists, clinicians, and consumer advocates, the PCRP has made strategic investments to align the renowned scientific, clinical, and institutional resources of major American Universities and Cancer Centers. Development of the Prostate Cancer Clinical Trials Consortium (PCCTC), Prostate Cancer Biorepository Network (PCBN), and North Carolina-Louisiana Prostate Cancer Project (PCaP) has accelerated the arrival of more effective treatments and better tools for detection, and enhanced our understanding of the racial disparities in prostate cancer. These PCRP investments are rapidly ushering in a new era of personalized medicine that will guide us towards the ultimate goal of conquering prostate cancer.

Revolutionizing the Clinical Management of Prostate Cancer through Innovation, Collaboration, and Precision Medicine Prostate Cancer Clinical Trials Consortium

Notable PCCTC Achievements:

- Establishment of a new limited liability company in 2014 – Prostate Cancer Clinical Trials Consortium, LLC – whose goal is to rapidly bring scientific discoveries to patients through multi-institutional clinical trials, while striving, through partnerships with industry, to achieve sustainability of the group into the future
- Addition of two new clinical sites in 2014 – Weil Cornell Medical College and University of California, Los Angeles – and continued investment in the consortium through 2017
- Substantial involvement in trials resulting in FDA approval of abiraterone (ZYTIGA®) and enzalutamide (XTANDI®), with another six agents that have advanced to Phase III clinical trials
- Completion of 108 clinical trials, with an additional 33 trials still active or pending activation
- Enrollment of over 4,447 patients to PCCTC trials, with 15% representing patients from minority populations



The PCCTC is a network of academic institutions in the United States committed to accelerating hypothesis-driven Phase I and Phase II clinical trials of promising new therapeutic agents and treatment approaches for clinical practice in prostate cancer.

The group was established in 2005 through the combined support of the PCRP and the Prostate Cancer Foundation, and it has received over \$52.1M in PCRP funding to date.

The PCCTC, under the leadership of Dr. Howard Scher at Memorial Sloan Kettering Cancer Center, has streamlined clinical trial development, activation, and execution processes. Capitalizing on their unique clinical expertise, patient populations, and scientific resources, PCCTC investigators at 13 major cancer research centers across the country have collaborated to establish scientific and clinical priorities to rapidly and successfully advance novel therapeutics through early (Phase I and II) clinical trials to large Phase III clinical trials. The consortium is also at the forefront of the personalized medicine arena, incorporating biomarker components into trials and implementing a clinical stages model of prostate cancer to ensure that each patient assigned to a study receives the optimal treatment customized to provide maximum benefit.

Strategic Partnerships



Opportunities for Resolving Prostate Cancer Health Disparities

North Carolina-Louisiana Prostate Cancer Project

The PCaP began in 2003 with the goal of understanding why AA men are twice as likely as men of other racial groups to be diagnosed with, and die from, prostate cancer. Under the direction of Dr. James Mohler, the PCaP brought together researchers from the University of North Carolina at Chapel Hill, the Louisiana State University Health Sciences Center, the Roswell Park Cancer Institute, eight other academic centers, and four government agencies. The project studied over 1,000 AA and 1,000 Caucasian American men newly diagnosed with prostate cancer in North Carolina and Louisiana. All of the patients were evaluated by health care professionals, and a database of socioeconomic, clinical, pathological, and epidemiological information was developed that annotates a biorepository of patient biospecimens. Today, the information and resources developed by PCaP continue to be updated with treatment and oncological outcome data, and this remains available to the prostate cancer research community via the PCaP database (<http://ncla-pcap.org/>) to fuel new studies regarding the biological and sociocultural factors underlying prostate cancer's disproportionate incidence and death rate among AA men.

Notable PCaP Highlights:

- Found that blood level of 25-hydroxyvitamin D is positively associated with prostate cancer aggressiveness in AA men with low calcium intake and inversely among men with high calcium intake.
- Published the first paper to demonstrate that the levels of thioredoxin 1 (an indicator of redox status) in prostate tissue are positively associated with Gleason score and inversely associated with dietary antioxidant intake.
- Found no evidence of racial differences in the initial treatment of prostate cancer after correcting for patient life expectancy and cancer aggressiveness as defined by treatment guidelines developed by the National Comprehensive Cancer Network.
- Found that 3 years post-diagnosis, younger AA men were more likely to experience treatment decisional regret than older AA men, and that 13% of all men experienced treatment decisional regret and were not satisfied with their understanding of the potential side effects of treatment.



Providing Critical Tissue Samples to Help Drive Prostate Cancer Research

Prostate Cancer Biorepository Network

The PCRFP initiated the PCBN in 2009 in response to the prostate cancer research community's need for human prostate cancer biospecimens. To achieve the program's goal of providing high-quality, well-annotated biospecimens for wide use by prostate cancer investigators, the consortium was tasked with developing optimized and standardized protocols for collecting biospecimens, fostering an infrastructure to facilitate the growth of this resource, and performing biospecimen science research to improve methods for biomarker studies.

The PCBN, under the direction of Dr. Bruce Trock, is a collaborative network of four participating institutions — the Johns Hopkins School of Medicine, the New York University Medical Center, the University of Washington, and Memorial Sloan Kettering Cancer Center — that have developed a biorepository of biopsy, prostatectomy, and body fluids along with corresponding pathology, clinical, and outcome data. The PCBN has a standardized mechanism for release of biorepository samples and data to researchers (details available at <http://prostatebiorepository.org>).

Notable PCBN Achievements:

- Established a resource containing samples from more than 3,400 prostate cancer patients, including blood, biopsy, prostatectomy, tissue microarrays, and metastatic tissues.
- Made available 23 prostate cancer tissue microarray sets for testing biomarkers associated with outcomes such as tumor grade/stage, biochemical recurrence, metastatic progression, racial disparity, hormone therapy resistance, and family history.
- Developed a rapid autopsy program that has collected very valuable and rare metastatic tumor specimens.
- Distributed samples to 55 prostate cancer investigators at 41 institutions in 5 countries.
- Dr. Bettina Drake and the Washington University joined the PCBN in 2015, providing specimens from prostate cancer patients on active surveillance, and with high-risk disease, particularly AA samples.
- PCBN biospecimens have been cited in at least 16 publications.

PCRP FY14 and FY15 Investments

Recognizing that men are living longer with prostate cancer, the PCRP in FY14 added a new overarching challenge to encourage investigators to develop strategies that optimize the physical and mental health of men diagnosed with and being treated for prostate cancer. The program re-offered a large variety of specialized award mechanisms focused on impact-driven or innovation-driven ideas, as well as mechanisms specifically designed for supporting younger investigators. To enhance the availability of rare human prostate cancer samples, the program offered to expand the Prostate Cancer Biorepository Network in FY14, from four to five institutions, by offering a new funding opportunity: the Prostate Cancer Biospecimen Resource Site Award. However, in FY15, the PCRP simplified its investment strategy by offering fewer mechanisms, but maintained its focus on supporting impact- and innovation-driven research ideas. Team science-driven studies were also encouraged through specific options within the mechanisms. In addition, as cancer research is highly data-intensive, language was added to all program announcements to promote applications from investigators in the disciplines of bioinformatics and bioengineering. In both FY14 and FY15, the program continued its support of new discoveries, and targeted efforts to resolve disparities in prostate cancer incidence, morbidity, and mortality.

Table 1. PCRP Investment Summary for FY14 and FY15

Focus and Award Mechanisms	FY14 Applications Received	FY14 Awards	FY15 Applications Received	FY15 Awards
Impact Research				
Biomarker Development Award	7	2	N/A	N/A
Clinical Exploration Award	9	0	N/A	N/A
Health Disparity Research Award	43	6	57	4
Laboratory - Clinical Transition Award	14	1	N/A	N/A
Population Science Impact Award	12	1	N/A	N/A
Impact Award	N/A	N/A	54	8
Exceptional Responders Award	N/A	N/A	6	0
Innovative Research				
Exploration - Hypothesis Development Award	235	24	N/A	N/A
Idea Development Award	305	40	326	47
Synergistic Idea Development Award	60	10	N/A	N/A
Training/Recruitment				
Collaborative Undergraduate HBCU Student Summer Training Program	6	4	9	5
Physician Research Training Award	8	6	8	5
Postdoctoral Training Award	89	25	73	23
Research Resources				
Prostate Cancer Biospecimen Resource Site Award	5	1	N/A	N/A
Total	793	120	527	92

N/A – Not offered that fiscal year

The Vision for FY16

In FY16, the PCRP received an \$80M Congressional appropriation for prostate cancer research, and the Programmatic Panel met to discuss prostate cancer and identify critical gaps in research funding. Even though today's patients with advanced prostate cancer have important new treatment options, resistance to these therapies remains of critical concern. Overall, the Programmatic Panel recommended retaining the streamlined investment strategy implemented in FY15, which included fewer award mechanisms while still maintaining the PCRP tradition of offering opportunities to support ideas driven by impact and innovation. All mechanisms are intended to support the basic, translational, and clinical research projects, with only the Impact Award available to support clinical trials. The PCRP also continues to encourage team science-driven projects by providing partnering or collaborating PI options for the Idea Development Award, Impact Award, and Health Disparity Award mechanisms. The program continued to offer award mechanisms specifically targeted to support mentored research opportunities for young investigators. Two mechanisms were renamed to increase emphasis on the research project as well as the mentored investigator: the Physician Research Award and the Early Investigator Research Award. The Idea Development Award also offers a separate New Investigators category. In addition, a Clinical Consortium Research Site Award will allow new institutions to join the PCCTC as clinical research sites; currently funded sites will also be encouraged to reapply for funding to remain part of the PCCTC. The following six award mechanisms were selected to maximize the impact of the FY16 PCRP investment toward eliminating death from prostate cancer and enhancing the well-being of men experiencing this disease.

Table 2. PCRP FY16 Vision (Award Mechanisms)

Focus	Award Mechanism
 <p>Impact</p>	<p>Health Disparity Research Award: Supports high-impact approaches to prostate cancer health disparity research with the potential to improve the understanding of, and ultimately contribute to, eliminating disparities in prostate cancer incidence, morbidity, mortality, and survivorship. Additional funding available for the Qualified Collaborator and/or Nested Traineeship Options.</p>
	<p>Impact Award: Supports the full spectrum of research projects or ideas that specifically focus on scientific and clinical prostate cancer issues, which, if successfully addressed, have the potential to make a major impact in eliminating death from prostate cancer and enhancing the well-being of men experiencing the impact of the disease. Additional funding available to Established Investigators for the Partnering PI Option.</p>
 <p>Innovation</p>	<p>Idea Development Award: Supports new ideas that represent innovative, high-risk/high-gain approaches to prostate cancer research and that have the potential to make an important contribution to the PCRP vision and mission. The New Investigator Option encourages investigators in the early stages of, or developing, independent prostate cancer research careers. Additional funding is available to Established Investigators for the Partnering PI Option provided the proposed research is supported by the unique expertise, experience, and abilities of each PI, and clearly defines the synergistic components that will facilitate and accelerate progress in a way that could not be accomplished through independent efforts.</p>
	<p>Clinical Consortium Research Site Award: Allows institutions to join the PCCTC as clinical research sites. Currently funded sites will be able to reapply for funding to remain part of the PCCTC.</p>
 <p>Young Investigators</p>	<p>Physician Research Award: Provides support for physicians with clinical duties to pursue mentored training experiences for careers at the forefront of prostate cancer research.</p>
	<p>Early Investigator Research Award: Provides research support for pre-doctoral graduate students and recent doctoral graduates to pursue training in prostate cancer research.</p>



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