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 $8 billion (B) in appropriations from its inception through fiscal year 2013 (FY13). 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 an Integration 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.

“I have been involved with the CDMRP’s PCRP since its inception, as peer reviewer and panel chair, and as an awardee of PCRP grants. From both perspectives, I believe that the program is invaluable not only to trainees and junior investigators, but to established investigators as well. It is administered in a highly efficient and fair manner that allows in-depth studies that have benefited, and continue to benefit, the field of prostate cancer research and, ultimately, the prostate cancer patient.”

David M. Lubaroff, Ph.D.
Professor, Departments of Urology and Microbiology
Associate Director, Holden Comprehensive Cancer Center
University of Iowa Carver College of Medicine
SUMMARY OF OUR HISTORY

In 1997, $45 million (M) dollars 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 $1.3B to the PCRP, including $80M in FY14. 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.

PCRP PRIORITIES – THE PCRP SEEKS TO PROMOTE:

• Support highly innovative, groundbreaking research
• Support high-impact research with near-term clinical relevance
• Sponsor multidisciplinary, synergistic research
• Fund translational studies to support the fluid transfer of knowledge between bedside and bench
• Invest in research on patient survivorship and quality of life
• Foster the next generation of prostate cancer investigators through mentored research
• Promote research on disparities in the incidence and mortality of 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
Moving the Prostate Cancer Field Towards Finding A Cure

INTEGRATION PANEL

PCRP Integration 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 Integration 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.

“The PCRP has played an integral role in funding basic scientific, translational, and clinical research in the fight against prostate cancer. Through this highly regarded program, funding has not only been provided for the development of novel drugs, epidemiologic tools, and diagnostic platforms, but it has provided a vital resource to the training of young, highly talented and motivated investigators to enter into the field of prostate cancer research.”

Philip M. Arlen, M.D.
President and CEO
Precision Biologics, Inc.
FY14 PCRP Integration Panel Chair

“I’ve been privileged to join my vision with an amazing group of cancer investigators, physician–scientists, basic researchers, urologic surgeons, epidemiologists, and survivors. All are working towards the ultimate goal to increase patient survival and improve the quality of life for men with prostate cancer. As a PCRP Integration Panel member, this has been a brilliant educational experience, providing a tremendous source of knowledge on prostate cancer. I’m honored to salute CDMRP for nurturing exciting new ideas and consistently supporting the collaborative efforts of investigators working together to apply state-of-the-art technologies in clinical settings for detection of prostate cancer and stopping the lethal course of the disease, until we find a cure.”

Natasha Kyprianou, Ph.D.
Professor and James F. Hardymon Chair in Urology Research
Departments of Urology, Molecular Biochemistry, Pathology, and Toxicology
University of Kentucky College of Medicine
FY14 PCRP Integration Panel Member
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:

- Developing better tools for early detection of clinically relevant disease;
- Distinguishing aggressive from indolent in men newly diagnosed with 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.

"The PCRP is unique in its ability to lead and to encourage innovative, cutting-edge investigations that might not otherwise be funded, that address problems faced by men with prostate cancer. We know that prostate cancer has a profound effect on the biopsychosocial well-being of prostate cancer survivors and their families. We are proud of our new overarching challenge to fund much needed research into the mental health issues faced by these men and those who love and care for them. Survivorship has been too long ignored, but we are making a major effort to rectify this issue."

Joel T. Nowak, M.A., M.S.W.
Director for Advocacy and Advanced Prostate Cancer Programs, Malecare Men Fighting Cancer, Together
Board of Directors - National Alliance of State Prostate Cancer Coalitions
FY14 PCRP Integration Panel Member
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.

“While not often appreciated, the role of the reviewer is in many ways no less important or valuable than that of the grant applicant. Funding the best science can only be accomplished if the reviewers recognize the importance of their role in the granting process, and perform their mission seriously, responsibly, and with rigor. Absent that, the best science/scientists go untapped.”

Neil H. Bander, M.D., Bernard and Josephine Chaus Professor of Urologic Oncology
Weill-Cornell Medical College and Memorial Sloan Kettering Cancer Center

“Participating as a consumer reviewer gives me an opportunity to present the patient/family point-of-view on forward-looking projects and ideas. As a 14-year survivor, reviewing has been sort of a ‘therapy by action.’ It is vital to me that the PCRP includes plans to effectively deal with the physical, and sometimes overlooked mental, well-being of prostate cancer survivors.”

Jerry Hardy
US TOO International

“As a prostate cancer survivor, I know all too well the importance of ongoing research for a cure for this disease. Prior to becoming a consumer reviewer with the PCRP, I never knew the depth and scope of the research involved with fighting prostate cancer. My participation with the PCRP has opened my eyes to the hard work and dedication that goes on behind the scenes to find a cure for this disease. Sharing my prostate cancer experience as a consumer reviewer is my way of helping to improve the quality of life for prostate cancer patients and ultimately work towards finding a cure.”

Robert Ginyard
ZERO - The Project to End Prostate Cancer

“It is my great honor and privilege to serve as a PCRP reviewer to ensure the innovation and impact of well-reasoned scientific proposals, and to help PCRP foster the development of new investigators. PCRP is the leading supporter of research for the development of new treatments for advanced prostate cancer. I strongly believe that the cutting-edge research supported by the PCRP will lead to improvements in the quality of life for prostate cancer patients and help lessen the ethnic gap in prostate cancer incidence and mortality.”

Ram I. Mahato, Ph.D.
Professor and Chair, Department of Pharmaceutical Sciences
University of Nebraska Medical Center
383 CONSUMERS AND 1781 SCIENTIFIC REVIEWERS HAVE PARTICIPATED IN PEER REVIEW THROUGHOUT THE HISTORY OF THE PCRP.

“"I’m a seven-year prostate cancer survivor and currently lead an US-TOO support group at a New Jersey hospital. I’ve participated as a consumer reviewer on five peer review panels over the last several years. In my opinion, we are lucky to have the PSA [Prostate-Specific Antigen] test; especially because it has led to some men being diagnosed that might otherwise have gone unchecked. Although a valuable diagnostic exists, it is still difficult to determine which men should be treated for their cancer. Over-treatment in men with indolent disease can lead to complications and significant expenses for the patient. This issue has not gone unnoticed by scientists, clinicians, and consumers with whom I’ve served on the peer review panels. PCRP has made it one of its priorities to designate some of the $80M in appropriations received over the past several years to identify and characterize factors which contribute to differences in indolent versus aggressive disease. It was invaluable for me to see investigators proposing studies to better understand the disease, and not be worried about the business of treating prostate cancer.”

Robert Hanlon
Malecare, Inc.

“It has been a pleasure to support the work of the PCRP program by serving as a scientific reviewer. The PCRP review experience is unique in that it involves not only scientists but also prostate cancer patients that serve as consumer reviewers. The combination of scientists and consumers on each review panel ensures that every application is evaluated not only on its scientific merits but also on its ability to significantly impact the lives of prostate cancer patients. This input from the consumer reviewers has influenced the way I think about proposals, and has helped each panel to identify applications that will truly move the field forward.”

LaMonica Stewart, Ph.D., Associate Professor, Meharry Medical College

“I have been a scientist reviewer for the CDMRP PCRP’s Health Disparities panel for several years. I am impressed that the CDMRP puts an emphasis on innovative research. It can sometimes be frustrating that biomedical research seems to be a very slow process as we continue to build bit-by-bit on existing knowledge. It is very exciting when a grant application proposes a new methodology or treatment that takes that extra unexpected step above the ordinary.”

Kathleen C. Torkko, M.S., M.S.P.H., Ph.D., Assistant Professor, University of Colorado, Denver

“When I took part in the PCRP this past year, I had been in remission for over six years. Reviewing the proposals and participating in the in-person evaluation sessions highlighted for me the extreme difficulties in dealing with recurring and resistant cancer. But the inventiveness and promise of the proposals we discussed also gave me great hope that significant progress may soon be made. It was frightening and invigorating. Three months later, my checkups revealed recurrence of cancer. What I learned and what is being discovered has taken on a new significance”

Robert Hanlon
Malecare, Inc.
Successes: Making Progress Towards a Cure

Despite major challenges in finding a cure for prostate cancer, the PCRP’s mission of supporting innovative ideas for high-risk/high-gain research has led to breakthroughs that have changed clinical practice, improved methods of detection and diagnosis, and enhanced treatment options for prostate cancer patients. PCRP-funded investigators are making significant progress towards understanding the complex molecular pathways that fuel prostate cancer growth and treatment resistance, translating basic science discoveries into clinical practice, developing noninvasive detection and diagnosis strategies, and advancing novel therapeutic options for all men that will eventually eliminate prostate cancer health disparities. PCRP-funded investigators are pushing the boundaries of science and breaking into new areas of exploration. The following are examples of highly successful prostate cancer investigations that have already or are likely to impact the lives of men with the disease.
Blocking T-Cell Co-Inhibitory Molecules to Improve Immune Response to Prostate Cancer

Xingxing Zang, M.Med., Ph.D., Albert Einstein College of Medicine of Yeshiva University

The T cells of the body’s immune system are major combatants against cancer; however, many tumors, including those from prostate cancer, have ways to block immune responses against them. Recently, a new member of the B7 family of immune blockers, B7x, was discovered, and it was found that B7x, and its closest homolog, B7-H3, were highly expressed by more than 90% of human prostate cancers. Patients with high expression levels of either molecule were significantly more likely to have their cancer spread, return back after treatment, and die at an earlier stage. These findings suggest that human prostate cancer cells may use B7x and B7-H3 to block the immune system, and drugs that counter their effects could be useful therapeutic agents.

With this in mind, and with support from an FY09 PCRP New Investigator Award, Dr. Xingxing Zang set out to elucidate the mechanisms which regulate immune responses, specifically those regarding B7x, and to translate that information towards the development of new therapeutic strategies for prostate cancer. During the investigation, Dr. Zang was able to show that prostate cancer cells expressing B7x displayed accelerated tumor progression in mouse model systems. Furthermore, the investigative team was able to develop several monoclonal antibodies (mAbs) that target B7x to reverse its effect. One of these mAbs, named 1H3, possesses dual activity by blocking B7x-mediated co-inhibition of the immune system’s T-cell, and by producing a toxic effect in cells to directly initiate cell death in tumors.

Dr. Zang plans on translating the team’s basic research findings to the clinical setting and seeks to move the results quickly into medical practice. Once humanized, the B7x-targeting mAbs should be ready for clinical trials to assess their ability to reverse the co-inhibition of T-cells and allow the immune system to attack cancerous cells without damaging normal tissues. The Albert Einstein College of Medicine’s Cancer Center has many project areas directly relevant to cancer immunology, and it provides a supportive infrastructure to help Dr. Zang move this PCRP-funded research closer to the clinic.
Optical Sensing of Microscopic Structures May Be Used to Grade Prostate Cancer and Predict Patient Outcome

Min Xu, Ph.D., Associate Professor of Physics, Fairfield University

Diagnosis and prognosis of prostate cancer from biopsy or prostatectomy specimens currently rely on histopathological evaluation to determine grade, stage, and surgical margin status. The Gleason score (GS) is the single-most important prognostic factor in prostate cancer. It is one determinant of a patient’s specific risk of dying from prostate cancer, and it strongly influences decisions regarding options for therapy. The majority of patients are now diagnosed with tumors of GS 6 and 7, and these tumors can take two distinct disease courses: indolent or highly aggressive, the latter of which leads to death if not treated. Although the GS is currently the most useful indicator for prognosis, it remains largely subjective. Furthermore, prostatic tissue must be removed in order to determine a GS, making the process invasive and therefore not ideal.

To overcome this problem, Dr. Min Xu, with funding from an FY09 PCRP New Investigator Award, is utilizing light backscattering, the diffuse reflection of light back in the direction of the source, to identify correlations between optical tumor characteristics, prostate cancer grade, and patient outcome. To accomplish this, he developed an enhanced backscattering tomography technique that generates a three-dimensional map of tissue cellular architecture and nuclear morphology based on light scattering. This system is sensitive enough to quantify subtle changes in tissue architecture and nuclear structure that accompany tumor initiation and progression. Using tissue microarrays constructed by Dr. Jonathan Melamed’s group at New York University, which was developed as part of the PCRP-funded Prostate Cancer Biorepository Network, Dr. Xu discovered that the optical characteristics of the nuclear region could be used to distinguish aggressive from indolent prostate cancer.

In hopes of bringing this research closer to helping current cancer patients, Dr. Xu is measuring more cohorts of prostate cancer tissue microarrays and will further validate the correlations between the optical parameters with the grade of cancer and patient outcome. He also plans to develop an optical risk score for prostate cancer diagnosis and prognosis at the end of the funding period. In sum, Dr. Xu's research is laying the groundwork for constructing a noninvasive tool to help clinicians determine the most appropriate treatment strategy for protecting both life and quality of life for individual patients.
PSMA Targeted Nano-Radioimmunotherapy Using Curcumin for Advanced Prostate Cancer

Subhash C. Chauhan, Ph.D., University of Tennessee Health Science Center

Advanced stage prostate cancer is largely untreatable with current therapies, indicating a strong need for improved prostate cancer treatment. Radioimmunotherapy (RIT) is a rapidly emerging therapeutic modality for the treatment of a wide variety of cancers. However, so far, in solid tumors such as prostate cancer, RIT has shown only partial success both in preclinical and clinical studies. The partial response of RIT in solid tumors is primarily due to reduced accessibility of radio-probes to the cancer cells and their inferior radio-sensitivity. Another therapeutic agent already under investigation for various cancer types of all stages, called curcumin, is also known for inducing radio-sensitization/chemo-sensitization in cancer cells. Taking advantage of this powerful pre-existing agent, a team of investigators at the Sanford Research/University of South Dakota led by Dr. Subhash C. Chauhan*, an FY07 New Investigator Award recipient, has undertaken a challenge to develop a novel therapy that combines nanotechnology with the unique aspects of both RIT and curcumin. The team has investigated the hypothesis that loading curcumin into nanoparticles (NPs) created to specifically target prostate cancer cells via an anti-prostate specific membrane antigen (PSMA) antibody will improve the effectiveness of treatment due to tumor cell uptake of the NP-antibody complex.

Dr. Chauhan's team has made significant progress to date towards their goal of developing a PSMA-targeted curcumin NP modality. First, they started by generating a biodegradable controlled drug delivery carrier, called nano-curcumin, using poly(lactic-co-glycolic acid). They found that this nano-curcumin formulation exhibits a higher therapeutic efficacy in cell proliferation and colony formation assays, and in a xenograft mouse model. The team then proceeded to add the anti-PSMA antibody to the curcumin-loaded NPs; they have been able to demonstrate efficient and reproducible chemistry for this new conjugate particle, and biodistribution experiments indicate that the PSMA-targeted particles have an enhanced tumor-specific accumulation. Additionally, Dr. Chauhan's team has developed additional curcumin NPs for imaging and treatment of prostate cancer, called multifunctional magnetic NPs. This novel and multifunctional magnetic NP formulation has been patented and published. Dr. Chauhan's studies to date support the feasibility and efficacy of an innovative nano-RIT approach for advanced prostate cancer treatment.

*Dr. Chauhan's lab is now located at the University of Tennessee Health Science Center in Memphis, TN
Vitamin D Deficiency Predicts the Outcome of Prostate Biopsy in African American Men

Adam Murphy, M.D., M.B.A., MSCI, Northwestern University

African American men have the highest incidence of prostate cancer compared to other ethnic groups and are more likely to be diagnosed with advanced stage prostate cancer, and African American men are 2.5 times more likely to die from the disease. One potential factor that might contribute to this disparity is vitamin D deficiency. Sunlight exposure is the major source of vitamin D for most men, but in African American men vitamin D synthesis is lower than in European American men due in part to the UV blocking effects of melanin in the skin.

However, it has been difficult to find a clear link between prostate cancer risk and vitamin D status because there are so many potential variables that affect both. Dr. Adam Murphy of Northwestern University, with funding from an FY09 PCRP Physician Research Training Award, under the guidance of Dr. Rick Kittles (University of Illinois at Chicago), proposed to perform the first clinical study of vitamin D deficiency and prostate cancer risk in African American and European American men limited to those undergoing their first prostate biopsy, which would help to reduce the number of variables and strengthen the ability to find associations between vitamin D and prostate cancer.

Dr. Murphy enrolled over 650 Chicago men, ages 40 to 79, who were going to have their first prostate biopsy after displaying an elevated PSA and/or an abnormal digital rectal examination. On the day they came to the clinic for their biopsy, Dr. Murphy collected a blood sample from each patient and determined the level of 25-hydroxyvitamin D in each. The vitamin D level was then compared to the results of the prostate biopsy. He found that severe vitamin D deficiency increased the odds of being diagnosed with higher stage and higher grade of prostate cancer in both African American and European American men, and that this association was even stronger among African American men. He also found that vitamin D deficiency is relatively common among men from Chicago, even those taking the recommended daily vitamin D allowance (600IU) through diet or supplements. Having established that vitamin D deficiency is linked to more aggressive prostate cancer, Dr. Murphy plans in future work to define how vitamin D affects prostate cancer progression, and will perform genetic studies to identify those men who are most likely to respond therapeutically to vitamin D.
Collaborative Summer Training Program for HBCU Undergraduates in Washington, DC

Shiv Srivastava, Ph.D., Uniformed Services University of the Health Sciences – Center for Prostate Disease Research
Deepak Kumar, Ph.D., University of the District of Columbia

Since its introduction in 2004, the goal of the PCRP’s Collaborative Undergraduate HBCU Student Summer Training Program Award has been to provide educational and training opportunities for HBCU undergraduate students at a critical decision-making point in their education, with the expectation that these trainees will pursue careers in prostate cancer research and thus increase the cadre of the next generation of researchers who will, in turn, make new discoveries and develop innovative treatments for prostate cancer.

Dr. Shiv Srivastava received an FY07 PCRP Collaborative Undergraduate HBCU Student Summer Training Program award to provide foundational cancer research opportunities for undergraduates at the University of the District of Columbia (UDC) through the Uniformed Services University of the Health Sciences (USUHS) – Center for Prostate Disease Research (CPDR). In this collaborative effort, Dr. Deepak Kumar served as the Partnering Principal Investigator at UDC. This program allowed UDC students with limited to no exposure in biomedical research to gain experience in state-of-the-art prostate cancer translational research.

Through the dynamic 10-week summer program at CPDR, students strengthened what they had already learned – in college science courses – by focusing on prostate cancer. They interacted with leading prostate cancer researchers, learned how to work effectively in teams, and developed the skills needed to present their research findings through regular seminars. Students also learned about the current trends in cancer research, including the biologic basis of prostate cancer health disparities.

This program has provided a gateway for students to pursue careers in biomedical and prostate cancer research. Ten (10) of the 16 students trained in the program are pursuing graduate/medical/professional schools, and they attribute their success to the UDC-CPDR program. Students have presented their research at various national conferences, including the PCRP’s IMPaCT meeting; they have also gone on to win several awards for their presentations.

In summary, this has helped expose UDC students to biomedical and prostate cancer research, guiding them into professional/graduate/medical schools, and providing them with the opportunity to join the biomedical workforce and develop into the next generation of prostate cancer researchers. Based on the program’s success, Drs. Srivastava and Kumar received another HBCU Student Summer Training Program award from the PCRP in FY13. This will ensure that current and future students at UDC will have the opportunity to participate in this valuable training program for several summers to come.
Development, Validation, and Dissemination of an Integrated Risk Prediction Model and Decision Aid to Discern Aggressive versus Indolent Prostate Cancer

Peter Carroll, M.D., M.P.H., University of California, San Francisco

Mortality rates for prostate cancer have fallen nearly 40% since the start of the prostate-specific antigen screening era, and are at their lowest level in the past 80 years. Despite this success, prostate cancer screening has become increasingly controversial, in large part due to high rates of diagnosis of low-risk, indolent prostate cancer that would likely never cause symptoms if remained undiagnosed. Overall, clinicians agree that not all prostate cancer must be aggressively treated, and that many men can be safely followed for years with active surveillance. However, in as many as 30% of cases, the cancer may turn out to be more aggressive than it appears at the time of diagnosis, limiting the number of men and their physicians who feel comfortable choosing active surveillance. As a result, many men choose to undergo surgery, radiation, and other treatments for low-risk prostate cancer, which may be unnecessary and may cause debilitating side effects.

Dr. Peter Carroll at the University of California, San Francisco (UCSF), believes that the answer to this problem is not to stop screening but rather to help men become better informed about their cancer, and how to decide on treatment. With support from an FY12 PCRP Transformative Impact Award, Dr. Carroll has assembled a multidisciplinary team of experts with long experience and success in prostate cancer risk assessment, biomarker validation, lifestyle/prevention research, decision support, quality of life assessment, genetic epidemiology, cancer psychology, and software development to revolutionize the management of low-risk prostate cancer. Additionally, this research team is leveraging the expertise and resources of two companies, which are industry leaders in cancer genetics analyses, and are working closely with prostate cancer advocates at UCSF and other clinical sites.

This multidisciplinary team is currently developing and validating a novel risk-prediction model to better inform men about their true risk for cancer progression. Additionally, the group is developing a decision support intervention that utilizes a website and live-coaching assistance from genetic counselors to aid men in their decision to treat or monitor their disease. They believe this effort will revolutionize initial prostate cancer management, leading to less overtreatment, less morbidity and suffering associated with treatment side effects, less anxiety and uncertainty, more knowledge, improved satisfaction, and better quality of life for the hundreds of thousands of men every year who must wrestle with this diagnosis.
Targeting the Aberrant Androgen Receptor in Advanced Treatment-Resistant Prostate Cancer
Stephen Plymate, M.D., University of Washington

New drugs, such as abiraterone and enzalutamide, that target tumor androgen production and the androgen binding domain of the androgen receptor (AR), have shown that the AR is an important driver of castration-resistant prostate cancer. In spite of the effectiveness of these treatments in the short-term, the tumors resume growth, and the majority of this growth continues to be driven by the AR. Dr. Stephen Plymate, of the University of Washington, and others had previously discovered a novel way that prostate cancers become resistant to these new drugs. This mechanism is due to the development of constitutively active AR-splice variants (AR-Vs). These AR-Vs lose an important piece of the AR called the ligand binding domain to which all current AR therapies are directed, and they lose the ability to interact with androgens. However, the AR without the ligand binding domain is constitutively active (i.e., no longer requires androgen) and has the unique capacity to constantly stimulate tumor growth.

With funding from an FY12 Transformative Impact Award, Dr. Plymate has assembled an international multi-institutional team of basic scientists and clinicians at the forefront of prostate cancer clinical trials to develop at least two new therapeutic agents (an HSP90 inhibitor and an AR amino-terminal inhibitor) that can inhibit AR-Vs and take them to clinical trials. These therapeutic agents were developed from preclinical studies in the laboratories of the investigators and are being carried out in collaboration with the pharmaceutical industry to expedite the transition to patient care. Although the project was only recently initiated, the investigators have already demonstrated that bone marrow biopsies from patients relapsing after treatment with enzalutamide or abiraterone show a clear nuclear AR localization indicating AR activity. The clinical significance of the AR-Vs in the development of resistance to enzalutamide has recently been highlighted (with PCRP funding) by one of Dr. Plymate’s co-investigators, Dr. Jun Luo of Johns Hopkins University, who demonstrated that the presence of AR-V7 splice variants in circulating tumor cells in blood samples indicated that the patient was resistant to enzalutamide, thus identifying a potential new predictive biomarker for treatment resistance. The research team includes Dr. Johann de Bono of the Royal Marsden Foundation Trust Institute of Cancer Research, London, who has played a major role in the clinical development of abiraterone and enzalutamide, and additional investigators at the University of Texas Southwestern, University of Minnesota, Fred Hutchinson Cancer Research Center, and University of Adelaide. This project fulfills the goals of the Transformative Impact Award by identifying the mechanisms AR-Vs use to bypass the current, most effective treatments for lethal prostate cancer, and by developing agents that can be directly translated to the targeted patient population to improve patient survival and quality of life within the near-term performance period.
Toward the Practice of Precision Medicine: A Biomarker Validation Coordinating Center

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

To revolutionize the clinical management of castration-resistant prostate cancer (CRPC), it is essential to develop targeted therapies in more precisely defined and biologically relevant patient groups. Recent advancements in drug development for CRPC have focused on targeting the two most frequently altered molecular pathways in prostate cancer: the androgen receptor (AR) and the phosphoinositide 3-kinase (PI3K) signaling pathways. Despite encouraging clinical success of targeting these pathways, no validated assays exist for the measurements of key predictive biomarkers to identify which patients would actually benefit from a specific treatment before it is administered. This shortcoming has resulted in the overtreatment of prostate cancer patients with drugs that are only designed to be effective in the subset of prostate cancer patients. Such blanket treatment can cause unneeded toxicities and, more broadly, hurts drug development and innovation. Currently, when a new targeted therapy is tested in a large, unselected patient population, it may only be successful in a small subset although not be U.S. Food and Drug Administration (FDA)-approvable based on the outcome in the population as a whole. Thus, a potentially effective new agent may not become available to the patients who need it. To overcome this issue and maximize the likelihood that a patient will receive an effective treatment, Dr. Howard Scher at Memorial Sloan Kettering Cancer Center is currently developing a Multicenter Assay Validation Program to coordinate the development of analytically and clinically validated biomarker assays to enable the right drug to be given to the right patient at the right time.

With support from an FY12 PCRP Transformative Impact Award, Dr. Scher has assembled a multidisciplinary team from five premier medical centers, bringing together leaders in prostate cancer pathology, medical oncology, computational biology, and statistics. This group has selected a set of five biomarker tests for the AR and PI3K pathways to develop validated assays that can predict a patient’s sensitivity to AR and PI3K inhibition. In addition, the team plans to validate five additional candidate markers, not necessarily limited to the AR and PI3K pathways, that have been identified through various discovery platforms. Dr. Scher hopes to use the assays in the near future as a part of the eligibility criteria for protocols evaluating novel agents and, separately, to guide the selection of approved agents that target these pathways. Successful deployment of such assays would allow patients to be given drugs that are most likely to benefit them while being spared the toxicities of ineffective therapies. Furthermore, identifying the patient population that would receive the highest benefit from certain treatments could help to accelerate clinical trials and rapidly move these treatments into clinical practice. By creating the only collaboration that brings together leaders in various fields of prostate cancer research to specifically address assay validation, Dr. Scher and his team intend to bring about an era of precision medicine where the choice of treatment is based on the real-time biologic profile of an individual patient’s tumor.
A Novel Microscopy Technique for Better Prostate Cancer Detection and Prognosis

Rohit Bhargava, Ph.D., University of Illinois

The presence of prostate cancer is usually first suspected through a PSA test result or a physical examination. Men who are suspected to have prostate cancer undergo a prostate biopsy, and the biopsy specimens are analyzed by a pathologist who examines the tissue under a microscope and identifies certain characteristics of the cells and tissue architecture that indicate the presence and potential severity of cancer. However, this long-established method of recognizing disease and predicting its progression is an imperfect science and subject to some interpretation, and misdiagnosis can put some patients at risk for allowing their cancer to develop to aggressive disease, or cause other patients to undergo unnecessary treatment for tumors that may never harm them.

At the University of Illinois, Dr. Rohit Bhargava has developed a novel form of microscopy that not only measures tissue structure, but also the chemical content of every cell. With support from an FY06 PCRP New Investigator Award, he was able to apply this method, termed infrared spectroscopic imaging, to analyze prostate tissue biopsies. Working with a team of engineers, surgeons, and pathologists, Dr. Bhargava developed sophisticated mathematical algorithms that allow him to look for cell types that determine the presence and severity of cancer with an accuracy that is unmatched by current methods. By looking at the chemical changes in each cell type present in the prostate tissue, this technique identified changes in specific cell types that correlated with a higher probability of recurrence, thereby identifying which patients would be more likely to develop advanced disease after treatment. These findings have now been validated on a large scale, and Dr. Bhargava plans to bring this new technique to multi-site clinical trials. Successful translation to the clinic could provide major benefits for prostate cancer patients in the near-term future.

(A) Conventional imaging in pathology requires dyes and a human to recognize cells.
(B) In chemical imaging data cubes, both a spectrum at any pixel (C) and the spatial distribution of any spectral feature can be seen, e.g., in (D) nucleic acids (left, at ~1080 cm\(^{-1}\)), and collagen specific (right, at ~1245 cm\(^{-1}\)). (E) Computational tools can then convert chemical imaging data to knowledge used in pathology.
IGF1R Targeting for Better Prostate Cancer Imaging and Therapy

Weibo Cai, Ph.D., University of Wisconsin, Madison

Prostate tumors have many differences from patient to patient, and even within an individual patient, multiple areas of tumor can differ from each other in many ways. This variance, especially within a single patient, creates significant challenges for successfully treating prostate cancer with a one-size-fits-all approach, and is the reason researchers have been pushing towards more personalized medicine. Enhanced, non-invasive imaging on a molecular level would be a key advancement for prostate cancer detection and diagnosis, and would be even further useful in ensuring the delivery of molecularly targeted drugs to the right patients at the right time with the right dose. The research team led by Dr. Weibo Cai at the University of Wisconsin, with funding from an FY10 PCRP Idea Development Award – New Investigator Option, is using their extensive experience in molecular imaging and cancer therapy to address this important issue.

Dr. Cai and his team have been working on developing a platform that would be used for both non-invasive imaging and molecularly targeted therapy. This platform is built around the insulin-like growth factor 1 receptor (IGF1R), the expression level of which is increased in some prostate cancer tumors and can be used for both imaging and therapeutic applications simply with the use of different radioisotopes for diagnostic or therapeutic purposes. This dual functionality can be exploited for major advancements in the clinical management of prostate cancer, since IGF1R-based agents would enable more accurate patient selection for IGF1R-targeted clinical trials and effective monitoring of therapeutic responses, and provide new candidate anti-cancer drugs.

Building on the successful results from his PCRP-funded project, Dr. Cai plans to continue moving this IGF1R platform closer to use for patients by using IGF1R-targeted positron emission tomography (PET) imaging tracers as diagnostic and prognostic agents, and by developing new radiotherapy agents. His goal is that this new agent would allow for initial screening of prostate cancer patients to identify those that might best benefit from IGF1R-based treatment, and subsequently treat those individuals with the IGF1R therapeutic agent by simply substituting the imaging isotope with a therapeutic isotope. This “scout-and-treat” strategy is expected to provide a significantly higher response rate in prostate cancer patients than conventional cancer therapies.

Serial PET images of DU145 prostate cancer xenograft-bearing mice after intravenous injection of a 64Cu-labeled anti-IGF1R mAb. A PET/CT fused image of the mouse at 24 hours post-injection is also shown. Arrowheads indicate the DU145 tumor.
Nowhere to Hide: Better Non-invasive Detection of Prostate Cancer Using Improved Imaging

Wubao Wang, Ph.D., City University of New York

Physicians routinely use two examinations to screen for prostate cancer: the PSA blood test and a digital rectal examination. An abnormal digital rectal exam and an elevated PSA level are both possible indicators of the disease; however, neither test by itself or in combination can provide a definitive diagnosis of prostate cancer. If either test is abnormal, physicians will usually perform an invasive biopsy procedure, which is painful and damaging to prostate and other tissues. Therefore, researchers are working to develop new diagnosis methods that will be both less invasive and more accurate.

Dr. Wubao Wang’s group at the City University of New York (CUNY) has been working to develop a less invasive imaging technique with support from an FY07 PCRP Idea Development Award. Dr. Wang said, “The key feature of our rectal scanning imager is the use of near infrared radiation to image the prostate through the rectum. This imaging approach will greatly improve and supplement current (detection) methods of PSA and digital rectal exam because the scanning imaging unit and inverse image reconstruction technique can be used to map the internal structure of the prostate, distinguishing cancerous from normal areas.”

This group has utilized 2D image acquisition software combined with an inverse image reconstruction algorithm to record sets of 2D images of the prostate in animal models and then subsequently determine the existence and 3D locations of cancerous sites. The group is now preparing to extend this testing to the clinical setting, evaluating the efficacy of rectal scanning imaging for prostate cancer diagnosis before ultrasound and biopsy measurements. In addition, Dr. Wang plans to incorporate the use of “smart” fluorescent dyes to target and mark prostate cancer receptors and cells, providing identification of aggressive metastatic cancers in early stages. These advanced methods for earlier and improved detection of prostate cancer will help physicians provide better prostate cancer management and protect patients with low-risk disease from unnecessary treatment.

The key investigators in the CUNY research group include Prof. Robert Alfano (Director of the Institute for Ultrafast Spectroscopy and Lasers), Dr. Wubao Wang, and Dr. Yang Pu. The research achievement was made in collaboration with Dr. James Eastham at Memorial Sloan-Kettering Cancer Center, Prof. Samuel Achilefu at Washington University School of Medicine, and Prof. Min Xu at Fairfield University.

Fig.1 (a) A photograph and (b) schematic diagram of the portable rectal NIR scanning polarization imaging unit.
Predicting Prostate Cancer Recurrence – Using Biomarkers to Guide Treatment Decision Making
Carlos S. Moreno, Ph.D., Emory University

When a man is diagnosed with prostate cancer, he and his physician must decide on the best course of treatment. Because not all prostate cancer will progress to aggressive disease, and any treatment comes with considerable side-effects, biomarkers that can predict the likelihood of recurrence are greatly needed to aid men and their doctors in deciding on the appropriate course of treatment. With funding from an FY09 PCRP Idea Development Award, Dr. Carlos S. Moreno at Emory University has identified and validated biomarkers that can help to predict the likelihood of prostate cancer recurrence after surgery. The next step in the process of translating his research to patients is to develop a clinical test that will be easy to use and will provide clear results. Ideally, these biomarkers would be used at the time prostate cancer is initially diagnosed through the use of biopsies. Dr. Moreno plans to test biopsies to determine if these biomarkers are predictive of outcome for patients who elect to undergo radiation treatment instead of surgery. If these biomarkers are helpful in this regard, they may help guide patients and doctors in the difficult decision-making process of whether to undergo radiation or surgery.

Another area of future research is to ensure that these biomarkers are accurate predictors for African Americans, who suffer from a very large disparity in prostate cancer incidence and outcome. Since many African American patients have more aggressive disease, and yet elect to have less aggressive therapy such as active surveillance, the information obtained from these biomarker tests could help guide patient counseling and therapy decision-making. For example, the patient whose biomarker data indicates a poor prognosis for radiation therapy, but a good prognosis for surgery, would clearly have a sound basis for electing to have a prostatectomy. The potential of these biomarkers to identify radio-resistant tumors could someday reduce the cancer-specific mortality for African American men and the disparities in outcome between African American and Caucasian prostate cancer patients over the long term.
Developing Better Predictors of Response to Prostate Cancer Treatment: Circulating Tumor Cells

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

Many treatment options for prostate cancer produce responses in only a subgroup of patients, but there is currently no way to predict which treatment is best for which patient. A specific type of tumor cell shed from both primary and metastatic tumors into the blood, called circulating tumor cells (CTCs), retain the intrinsic properties of the tumor, making them ideal candidates to serve as molecular biomarkers of treatment response in an effort to better “personalize” medicine.

Stemming from the observation in abiraterone acetate (ZYTIGA®) trials that patients with metastatic CRPC responded in variable patterns ranging from dramatic to intermediate to resistance after prolonged therapy, Dr. Daniel Danila, an FY08 Physician Research Training Award recipient, and his mentor Dr. Howard Scher led a team at the Memorial Sloan Kettering Cancer Center to address the mechanism of resistance for patients treated with abiraterone acetate. Their approach included predicting the association between tumor sensitivity to abiraterone treatment and molecular biomarkers detected in the CTCs collected from patients with metastatic prostate cancer. Dr. Danila and his team were able to demonstrate not only the feasibility of molecular profiling CTCs as a surrogate for sampling tumor tissue, but also that a significant proportion of abiraterone-treated patients have alterations of the prostate-specific fusion protein called TMPRSS:ERG. Important for clinical translation of these results, they also developed standard operating procedures for sample processing to ensure the validity of CTC assays.

Drs. Danila and Scher are now working to assess the potential correlation between TMPRSS:ERG with other factors (phosphatase and tensin homolog [PTEN], PI3K, genomic copy number variations) in determining tumor sensitivity to treatment. Furthermore, their team is working to validate these assays to ensure their robustness and reproducibility in order to optimize the chance to ultimately incorporate the biomarker results in medical decision-making, after testing them in conjunction with the clinical development of new targeted prostate cancer therapies being studied at Memorial Sloan Kettering Cancer Center and within the DoD PCRP-funded Prostate Cancer Clinical Trials Consortium. The concurrent development of these CTC assays with the development of novel AR targeting agents will enable clinicians to prospectively identify patients most likely to benefit from treatment, which will not only accelerate the development of new AR targeting agents, but ultimately will improve patient outcomes from prostate cancer treatment.
On the Path to Understanding, Identifying, and Eliminating Advanced Prostate Cancer: A Global Approach to Finding Key Mutations

Jay Shendure, M.D., Ph.D. (top), University of Washington
Peter Nelson, M.D., Fred Hutchinson Cancer Research Center

Fundamentally, normal cells transform into cancer cells as a result of underlying changes in the genetic code of the cell. Researchers have attempted to identify and characterize the genetic changes that cause cancer, and new technologies that have reduced the cost of these types of studies provide the potential for even greater strides in prostate cancer genetic research. Funded by an FY09 PCRP Synergistic Idea Development Award, a team of researchers led by Dr. Peter Nelson at the Fred Hutchinson Cancer Research Center and Dr. Jay Shendure at the University of Washington have conducted the first comprehensive assessment of every gene in the genome of advanced, lethal metastatic prostate cancer. While a considerable amount of research into the genome of primary prostate cancer has been done, significantly less is known about the genomes of metastatic prostate cancers.

By taking advantage both of new emerging technologies and the outstanding resources available at their institutions, such as the University of Washington's Biospecimen Repository for Prostate Cancer Research, Drs. Shendure and Nelson have used a mouse xenograft model to discover a number of potentially key genetic alterations that may contribute to the development of advanced disease. One of the most interesting findings was the discovery of three aggressive “hypermutation” tumor types with 10 times the number of genetic mutations previously found in other advanced prostate cancers. These mutations should provide insight for understanding and identifying lethal prostate cancer, and could be used to develop screening tests for early detection or drug targets to slow or stop cancer growth.

They also found thousands of individual, or “personal,” mutations unique to individual tumors, including several mutations that were associated with cancers resistant to testosterone suppression, a common treatment for advanced prostate cancer. This type of information could be extremely valuable in identifying which patients might be more likely to respond to testosterone suppression, preventing unnecessary treatment for other patients. These discoveries are important for facilitating additional insight into the biology of prostate cancer and ultimately the development of more effective therapies.

Approach to identify genes involved in castration resistance.
Personalized Risk Assessment for Adverse Effects after Radiation Treatment for Prostate Cancer

Barry Rosenstein, Ph.D. (top), Mount Sinai School of Medicine
Harry Ostrer, M.D., Albert Einstein College of Medicine

Great advances have been made in recent years to improve radiation therapy for prostate cancer. One such improvement involves being able to more specifically limit the radiation dose to the prostate cancer tissue, meaning that normal tissues can be better protected from the damaging effects of the radiation therapy. However, even with the improvements made, some amount of normal tissue still receives a substantial dose of radiation during the course of therapy. This exposure can result in toxicity that compromises urinary, rectal, or sexual function. In addition, these toxicities can vary between patients who receive seemingly identical radiation treatment, leading to the hypothesis that genetic factors may influence radiation response. Therefore, Dr. Barry Rosenstein at Mount Sinai School of Medicine and Dr. Harry Ostrer at Albert Einstein College of Medicine have been working together to create an assay based upon personal data and genetic markers capable of predicting which men are at greatest risk for developing complications after prostate cancer radiotherapy.

With support from an FY07 PCRP Synergistic Idea Development Award, they have been able to successfully identify over 100 different genetic markers, called single nucleotide polymorphisms (SNPs), that correlate with adverse effects upon urinary, rectal, and sexual function in patients treated with radiation therapy. By bringing together a team of investigators with a wide range of scientific and clinical expertise in areas such as radiation biology, radiation oncology, genomics, and urology, Drs. Rosenstein and Ostrer have created a research group capable of translating these types of findings from the lab to the clinic. And, as leaders in the field of “radiogenomics,” they have also worked to create the international Radiogenomics Consortium, including 157 investigators at 82 institutions in 19 countries, for the purpose of sharing biospecimens and data, enabling the type of large-scale studies essential for development of a predictive assay. With these types of translational resources, Drs. Rosenstein and Ostrer plan to complete the development of a robust, validated, sensitive, and specific clinical assay capable of predicting the risk for development of erectile dysfunction, urinary morbidity, or rectal injury following radiation treatment for prostate cancer, which will have a major impact on improving the survivorship and well-being of millions of men undergoing treatment for prostate cancer.

A predictive assay based on genetics could be used to identify the subset of patients at increased risk of developing adverse effects.
“From the beginning of the program, the PCRP has invested in research to address prostate cancer health disparities. Some of the most significant advances in solving the problem of prostate cancer have resulted from research projects funded by the DoD PCRP. A key focus of the program has been to shed light on why some populations such as African American men have disproportionately higher disparities in prostate cancer incidence and mortality compared to Caucasian American men. Although some factors such as race and ethnicity, biology, socioeconomic status, or access to care are known to contribute to prostate cancer disparities, there are still many unknowns. The PCRP has made significant investments in a diverse portfolio of behavioral, epidemiological, clinical, and basic research to gain knowledge to direct new and innovative strategies for better detection, prevention, and treatment of all men, and one day the elimination of all disparities. As an Integration Panel member and 17-year survivor, I am proud to be a part of this effort.”

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

Effect of Diabetes and Obesity on Disparities in Prostate Cancer Outcomes

Bettina Drake, M.P.H., Ph.D., Washington University

Unfortunately, there are no well-established methods for preventing prostate cancer. Some known risk factors for prostate cancer cannot be modified: older age, a family history of prostate cancer, and being an African American male. Therefore, identifying risk factors that men can manage or modify in order to reduce their risk of prostate cancer is important. Type II diabetes and obesity are two risk factors that can be managed with medication and modified through weight loss, and these have promising data on their impact on prostate cancer recurrence. Previous studies have indicated that prostate cancer risk increases shortly after the diagnosis of type II diabetes, but decreases as the duration of type II diabetes increases. This tends to be more evident for more aggressive prostate cancer. Therefore, to better understand how the risk factors of type II diabetes and obesity relate to prostate cancer outcomes, research must focus on how the type II diabetes is managed, as well as on the duration and timing of obesity and type II diabetes. In light of existing disparities in prostate cancer incidence and mortality, African American men are a priority audience for the basic science and epidemiological studies needed to evaluate the impact of these risk factors on prostate cancer recurrence.

Dr. Bettina Drake received an FY13 PCRP Health Disparities Research Award to explore the association between obesity, type II diabetes, and prostate cancer recurrence. She is working with a transdisciplinary team of well-established scientists and is utilizing the Department of Veterans Affairs prostate cancer cohort, which has the quality of data needed as well as an adequate African American population to assess potential racial differences. Results from this study will give high-risk prostate cancer patients information they need to make lifestyle changes. Obese and diabetic prostate cancer patients are of particular focus in this study. As Dr. Drake noted, “If we determine that certain populations with type II diabetes are at greater risk of adverse prostate cancer outcomes, then developing and implementing strategies to prevent or manage type II diabetes and reduce obesity among prostate cancer patients could be an important and efficient strategy to reduce their disease burden.”

Dr. Drake was also a recipient of an FY08 PCRP Health Disparity Training Award. This award provided her with the protected time and resources to train under an established prostate cancer health disparity researcher. This training and research experience contributed to her obtaining an assistant professorship and additional funding, including her FY13 Health Disparities Research Award.
Racially Associated Immunoglobulin G and FcGamma Receptor Genes and Humoral Immunity to Mucin 1 in Prostate Cancer

Janardan P. Pandey, Ph.D., Medical University of South Carolina

African American men are more likely to develop prostate cancer than Caucasian men, and they are also nearly 2.5 times more likely to die from the disease. Eradication of this disparity requires a better understanding of the underlying causes, which includes race, age, biology, socioeconomic status, or cultural influence. To date, it is known that genetic factors play a major role in susceptibility to prostate cancer, and scientists are actively searching for a connection to explain how this type of disparity affects men. For instance, a diverse distribution of certain susceptibility genes among various racial groups may, at least in part, account for the observed racial disparity in incidence and mortality between African American and Caucasian men.

The PCRP granted Dr. Janardan Pandey an FY09 Health Disparity Research Award for Established Investigators to support his study of several immunogenetic mechanisms that possibly contribute to the observed racial disparities in prostate cancer. Using blood samples from cancer patients and healthy controls, Dr. Pandey’s group discovered that particular variants of immunoglobulin GM (gamma marker) and FcγR (Fcgamma receptor) genes interact with each other, and thus constitute risk/protective factors for the development of prostate cancer. These genes also regulate “natural” immunity to prostate cancer-associated antigens mucin 1 and cyclin B1. Most importantly, a particular combination of GM and FcγR genes appears to be more potent in killing prostate cancer cells. For instance, the GM genotype associated with the highest level of antibody-dependent cell-mediated cytotoxicity (killing) of prostate cancer cells expresses the GM 3 allele. This allele is rare in African Americans, which might adversely influence their immunological ability to kill the cancer cells.

Dr. Pandey reasons that further characterization of these genes is essential given their marked racial differences in distribution. To date, an abundance of research is evaluating the role of genetically engineered immunoglobulin variants for immunotherapy, and Dr. Pandey believes that evaluation of the role of these and other naturally occurring variants might unveil novel pathways of immunity to cancer, leading to more potent immunotherapeutic strategies against prostate cancer.
The Impact of Prostate Cancer Treatment-Related Symptoms on Latino Couples

Sally L. Maliski, Ph.D., University of California, Los Angeles

Treatment for prostate cancer carries a number of side effects that can have a negative impact on men’s quality of life including erectile dysfunction, incontinence, and a diminished desire for sexual relations. Because of this, prostate cancer is often considered a couples’ disease, and partners have been shown to be important in prostate cancer decision making, helping men manage their treatment-related symptoms, and providing support. Prostate cancer is the most commonly diagnosed cancer among Latino men, and Latino men are more likely to be diagnosed with later stages of the disease. Little is known about how Latino couples experience and manage prostate cancer treatment and its side effects. In addition, people with low incomes tend not to have insurance and may not have access to health care. Thus, there is little information to guide the development of interventions to help low-income Latino couples manage prostate cancer and its symptoms, even though their need is great.

Dr. Sally Maliski was awarded an FY06 PCRP Health Disparity Research Award to study the impact of prostate cancer treatment-related symptoms on low-income Latino couples. In this study, couples were interviewed in depth, separately, at 6–12 months, 14–24 months, and 24–36 months after the man’s surgery, using questionnaires that asked about the man’s urinary, bowel, sexual, and hormonal symptoms, behaviors regarding diagnosis and treatment, and about his/her relationship with his/her partner. Data from these interviews and sociodemographic characteristics were analyzed to understand how Latino couples manage prostate cancer treatment and its side effects. Dr. Maliski found that Latino men had very little understanding of the side effects of androgen deprivation therapy, especially those related to increased cardiovascular and metabolic risk. Additionally, while the men in this study had access to prostate cancer treatment through a state-funded treatment program, there were other barriers to access such as language, difficulty in navigating public health care systems, and low health literacy. Latino men, by and large, are not amenable to a group discussion approach related to prostate cancer, use spirituality to cope with the disease, and develop ways to maintain their sense of masculinity despite prostate cancer side effects.

The Latina wives of Latino men see their role as stabilizing and normalizing the family, home, and marriage in the face of the changes wrought by prostate cancer. Wives are in charge of their husbands’ diets, which are important to urinary, cardiovascular, and endocrine function, and are uniquely poised to help their husbands cope with sexual dysfunction. The wives have little support and conceal distress from their husbands so as to not add to the burden of prostate cancer. This supports literature conducted with higher income Caucasian couples in which spousal caregivers have been observed to experience higher distress than their husbands who are prostate cancer patients.

Information from this study will be critical to the development of interventions for managing the symptoms of prostate cancer treatment that are specific to the culture and needs of low-income Latino couples.

Factors influencing the normalization efforts of Latina wives supporting Latino husbands recovering from prostate cancer surgery.
Integration Panel Perspective

“The PCRP has provided hope to men with prostate cancer. As a prostate cancer Warrior, I find hope and inspiration from the researchers and clinicians who are dedicating their lives to defeating prostate cancer. Substantial progress has been made in treating men due to the bold mission of the PCRP to fund research to eliminate death and suffering from prostate cancer, but there still is no cure. Despite the great improvement in new options for treatment, they primarily provide “survival” benefit, not a cure. Because there still is no cure, we need more research to focus on novel therapeutic options. The cure is out there. We just need to keep looking for it. If we do what we always did, we’ll get what we always got.”

James Kiefert, Ed.D.
Director Emeritus, Us TOO International

Novel Synthetic DNA Designer Molecules as Effective Therapeutic Agents against Prostate Cancer

William Gmeiner, Ph.D., and Jamie Jennings-Gee, Ph.D., Wake Forest University Health Sciences

The ideal treatment for prostate cancer is specific targeting of the cancer cells while leaving the normal cells of the prostate unharmed. Dr. William Gmeiner’s research team at Wake Forest University Health Sciences has been focused on just this: designing new drugs and novel drug delivery strategies that will specifically target prostate cancer cells and therefore minimize toxic effects to non-cancerous cells. With the support of an FY09 PCRP Idea Development Award, they have been able to develop a new combinatorial therapeutic strategy to improve the treatment of prostate cancer by taking advantage of a distinguishing cancer cell characteristic – low intracellular zinc levels.

In order to specifically deliver chemotherapeutic agents to cancer cells, Dr. Gmeiner’s team first tested the utility of DNA as a drug delivery vehicle. Special, highly structured DNA molecules were designed and shown to be capable of delivering toxic drugs to prostate cancer cells. The next step was to apply this DNA delivery system to the delivery of other agents that would specifically target the cancer cells, leaving the normal prostate cells unharmed. Since prostate cancer cells have lower zinc levels than normal prostate cells, combining zinc compounds with the DNA delivery vehicle resulted in specific delivery of the compound to the prostate cancer cells, and subsequently increased the cancer cells’ sensitivity to chemotherapy.

Dr. Gmeiner is now working on combining this DNA-zinc targeted therapy with another agent developed by his lab, a unique polypyrimidine agent called F10. In contrast to conventional chemotherapy, which can have seriously debilitating effects on patients’ quality of life, the results to date of cell treatment with F10 indicate that this compound causes minimal systemic toxicity. By combining this less toxic chemotherapeutic agent with the delivery potential of the DNA vehicle with the cancer cell targeted zinc compound, Dr. Gmeiner’s research will result in a new treatment approach that more cleanly separates the anti-cancer activity of these drugs while minimizing the systemic side-effects of other traditional approaches.
Clinical Testing of the Radiolabeled Anti-PSMA Antibody J591 in Patients with Non-Metastatic Castrate-Resistant Prostate Cancer

Scott Tagawa, M.D., Weill Cornell Medical College

Many men with prostate cancer suffer from biochemical relapse (rising PSA) after surgery and/or radiation. Hormonal therapy can control this state of disease temporarily, but most men will continue to have PSA levels that continue to rise. This state represents micro-metastatic disease, meaning tiny tumors that are in the body but too small to see by traditional imaging (CT, MRI, or bone scans). To address this, and to also address the need for better treatments for advanced prostate cancer, Dr. Scott Tagawa, using support from an FY08 PCRP Clinical Trial Award, has collaborated with a research team led by Dr. Neil Bander at Weill Cornell Medical College to develop an antibody, J591, which specifically recognizes PSMA, allowing prostate cancer cells to be targeted in a very specific manner.

PSMA is a cell-surface protein expressed by the vast majority of prostate cancer cells and generally not present elsewhere in the human body. By attaching J591 to a tiny radioactive particle (177Lu), a small amount of radiation is delivered to the cancer cells and can be used for treatment of tumors or for imaging to visualize tumors. The research team has been utilizing J591 in patients with metastatic prostate cancer for over a decade, with success in targeting metastatic tumors and benefitting patients with decreases in PSA, tumor size, and pain symptoms. Their Clinical Trial Award has allowed them to expand on the clinical testing of J591 through a multi-site, Phase II clinical trial combining hormonal therapy with targeted J591 radiation, bringing the radiation particle to unseen tumors. The group is also testing to see if a specialized type of a scan using the radiolabeled antibody can visualize these small sites of cancer that cannot be seen on standard scans.

To date, the trial has opened at various sites across the country and has shown that some of the men with non-metastatic prostate cancer treated with 177Lu-J591 have benefitted in terms of PSA reduction, with good tolerance to the treatment. It is hoped that the treatment will either prevent or delay the onset of metastatic disease. The investigators have leveraged the funds from the PCRP Clinical Trial Award among a large group of collaborative researchers (see photo) to move this exciting new treatment forward. Plans are underway to initiate a Phase III study to move radiolabeled J591 closer to possible FDA approval.
Crossing Barriers with an Enhanced Drug Delivery System for Prostate Cancer Therapy
Jan Schnitzer, M.D., Proteogenomics Research Institute for Systems Medicine (PRISM), San Diego

To be effective, anticancer drugs must pass through blood vessel walls in the body before they can reach and destroy tumor cells. Only a tiny portion of the drug dose ever reaches the inside of a tumor. One way to deal with the blood vessel barrier is to develop therapeutics that are smaller in size, making it easier for these to cross the blood vessel walls; however, these drugs tend to enter and harm both cancerous and normal tissues, resulting in unwanted and even lethal side effects. This lack of selectivity in the drug’s delivery and toxic effect has led scientists to try to create drugs engineered with tumor-specific identifiers, allowing them to target only cancer cells and spare normal cells. Yet these drugs, despite being well-designed to interact only with tumor cells, are still impeded by blood vessel walls and are prevented from reaching and killing their target cells.

Dr. Jan Schnitzer, with funding from an FY10 Idea Development Award, sought to discover a “portal” to help targeted therapeutics specifically cross tumor blood vessel walls. His lab at PRISM in San Diego made the key discovery that specialized cell membrane structures, called caveolae, function as pumps and display their own set of tumor-specific identifiers that can be targeted. Dr. Schnitzer’s team generated an antibody that only recognizes a special tumor caveolae protein, called Annexin A1. Animal experiments demonstrated in vivo that the Annexin A1 antibody rapidly targeted tumor caveolae, which pumped it across the blood vessel wall to penetrate prostate tumors. Toxic anti-cancer drugs were tethered to this antibody to deliver and concentrate their killing power only inside the prostate tumors, which shrank rapidly after a single intravenous injection. The fact that this antibody delivery system was able to enhance therapeutic potency greater than 100-fold is quite significant, because this will allow for very low, nontoxic drug doses while still maintaining treatment effectiveness.

Dr. Schnitzer states, “This breakthrough provides new hope that drugs can be effective yet not toxic because now they can concentrate inside tumors to actually reach their intended targets – the tumor cells deep within the tumors.” While this new therapeutic approach must be tested in human clinical trials, Dr. Schnitzer’s discovery demonstrates a potential paradigm shift in prostate cancer therapeutics that would increase not only patient survival but also patient quality of life by decreasing harmful side effects.
Working the Pipeline: From Understanding Molecular Mechanisms of Prostate Cancer to Advancing New Therapeutics Toward the Clinic

Stephen Balk, M.D., Beth Israel Deaconess Medical Center, Harvard Medical School

Major advancements in prostate cancer therapeutics have led to the recent FDA approval of multiple new chemotherapeutic agents, including abiraterone (ZYTIGA) and enzalutamide (XTANDI). While the availability of new agents such as these provides great hope for patients in the treatment and potential cure of their prostate cancer, not all patients respond positively to the same treatments, and even patients that respond positively at first can develop a lethal, resistant form of the disease. Thus, it is clear that while the field has made significant achievements in bringing new drugs to the market, the effort to find new agents to combat this disease is still critically needed.

Dr. Stephen Balk, a professor at Harvard University and PCRP-funded investigator, has dedicated his scientific career to unraveling the molecular mechanisms underlying prostate cancer development and using this information to improve upon current therapies and identify new therapeutic approaches. As the AR plays a central role in prostate cancer development, and androgen deprivation therapy is the standard initial systemic treatment for prostate cancer, a major focus of his lab's work has been exploring how the AR functions and how prostate cancers develop resistance to androgen deprivation therapy. Over the past decade, Dr. Balk's PCRP-funded research has extended well beyond the AR, leading to the advancement of therapies targeting additional pathways that drive prostate cancer development and the potential for immunotherapy.

After producing compelling data that the AR was reactivated in CRPC, Dr. Balk received an FY06 Idea Development Award to further study androgen metabolism and its role in the progression of cancer cells to the lethal CRPC disease state. His study led to the major finding that after androgen deprivation therapy (chemical or surgical castration), prostate tumors can acquire the ability to synthesize their own androgens in the absence of testicular androgens, thereby reactivating the AR. This discovery eventually led researchers to develop therapeutics that more effectively block androgen synthesis and AR activity, and ultimately resulted in the discovery and development of abiraterone and enzalutamide. Dr. Balk continues his work on improving the efficacy of these FDA-approved agents, and he is developing new approaches to target the AR through further investigation of the molecular mechanisms that contribute to relapse after abiraterone treatment, which is a study supported by an FY10 Idea Development Award.

Dr. Balk has also received multiple PCRP awards to facilitate his study of the PI3 kinase pathway for potential therapeutic targeting. Preliminary data from his lab demonstrating that this pathway was activated in prostate cancer (commonly due to PTEN loss) and that a cytoplasmic tyrosine kinase protein, called BMX, was activated downstream of this pathway led to an FY08 Idea Development Award to further investigate the preclinical potential of BMX inhibitors. The results from this study demonstrated that inhibition of BMX can suppress prostate cancer growth in mouse xenograft models, making BMX a good candidate for further therapeutic development. To move this work closer to the clinic, Dr. Balk is collaborating with Dr. Nathaneal Gray of the Dana-Farber Cancer Institute to conduct additional preclinical studies evaluating drugs that enhance BMX inhibitors for prostate cancer treatment.

Another area that has captured Dr. Balk's attention is the prominent role of gene fusion in prostate cancer, and an FY10 Idea Development Award has supported his investigation into the potential of ERG as a therapeutic target in advanced prostate cancer. This project stemmed from previous data showing that approximately half of all prostate cancers have
high levels of the ERG oncogene due to the TMPRSS2:ERG gene fusion. His lab discovered that the role of this gene fusion in prostate cancer cells was to induce expression of an oncogenic transcription factor called SOX9, and he showed that depletion of SOX9 from these cells dramatically reduced tumor growth and invasion, whereas overexpression of SOX9 in prostate cancer cells lacking the gene fusion increased tumor growth and invasion. These studies established a major pathway activated by the TMPRSS2:ERG gene fusion in prostate cancer, and Dr. Balk is currently focusing his efforts on new approaches to target the SOX9 protein.

Dr. Balk’s search for new therapeutic targets has also led him to investigate the potential of immunotherapy for advanced prostate cancer. Preliminary results suggested that a subset of immune cells called “invariant natural killer T (iNKT) cells” can be induced by alpha-galactosylceramide (alpha-GalCer), a compound isolated from a marine sponge. With funding from an FY08 Laboratory – Clinical Transition Award, designed specifically to help advance promising therapeutics from the laboratory bench to the clinic, Dr. Balk and Harvard University co-investigators Drs. Martin Sanda and Mark Exley demonstrated that alpha-GalCer can serve as an activating ligand for iNKT cells and, in combination with interleukin-12 (IL-12), can stimulate potent immune responses and enhance the efficacy of a prostate cancer vaccine in preclinical models of recurrent prostate cancer. Currently, Dr. Balk’s group is exploring ways to incorporate iNKT cell-activating ligands into prostate cancer vaccines to advance this enhanced therapeutic strategy closer to clinical use.

From ARs to gene fusions to immunotherapy, Dr. Balk and his team have utilized PCRP support over the past decade to make significant advancements in the understanding of molecular pathways and the development of novel therapeutic targets that have already had a major impact on the field of prostate cancer treatment.

“The PCRP is unique as its major focus is on research that will have an impact on patients with prostate cancer. My major motivation is, similarly, to conduct research that will have an impact on patients, and the PCRP has been a critical source of support for my work,”

Stephen Balk, M.D.
“Mechanisms of Resistance is an important PCRP Focus Area. Prostate cancer cells depend on androgens for their survival. Thus, androgen deprivation therapy is the primary treatment for advanced prostate cancer. Such therapy is effective in delaying progression of the disease. However, with time, tumors continue to grow as CRPC. How can CRPC survive and grow in the face of castrate levels of androgens? The PCRP has funded innovative research that has identified cellular and molecular mechanisms of resistance to androgen deprivation therapy. These discoveries are providing new therapeutic targets for the treatment of CRPC.”

Donald J. Tindall, Ph.D.
Carl Rosen Professor in Urology, Departments of Urology and Biochemistry and Molecular Biology, Mayo Clinic College of Medicine

Androgen Receptor Identity Crisis Promotes Resistance to Second-Generation Antiandrogens

Vivek Arora, M.D., Ph.D., Memorial Sloan Kettering Cancer Center

Antiandrogen therapy is the mainstay of treatment for advanced prostate cancer; however, in many cases, resistance to both the old and new antiandrogen therapies inevitably develops, and the cancer re-emerges as a result of increased expression or mutation in the AR or the enzymes that synthesize androgens. Dr. Vivek Arora proposed to decipher the clinically relevant mechanisms of resistance to the FDA-approved second-generation antiandrogen enzalutamide. With funding from an FY10 Physician Research Training Award, Dr. Arora developed a prostate cancer model in which human prostate cancer tissue was transplanted into mice; after treating the mice for several months with enzalutamide, he was eventually able to isolate prostate tumors that grew in the presence of the drug, thus displaying resistance to enzalutamide. Using a variety of molecular technologies to identify the drivers of resistance, he found that in many of the resistant tumors, AR inhibition caused glucocorticoid receptor (GR), a closely related hormone receptor, to be massively turned on, suggesting that the GR might be replacing AR. When he treated these enzalutamide-resistant prostate cancer cells with an anti-glucocorticoid drug (compound 15) that inhibits or depletes (knocks down) the GR, he observed that growth of these tumors was restrained, suggesting that combined inhibition of both the GR and the AR could prolong the duration of response to next-generation AR inhibitors in some patients. Unfortunately, the drugs in clinical use that target and inhibit the GR also activate AR and are unlikely to be very effective, therefore Dr. Arora’s current work includes a focus on development of new drugs for treating antiandrogen-resistant prostate cancer.

The Prognostic Potential of microRNA in Prostate Cancer

Shawn Lupold, Ph.D., Johns Hopkins University

MicroRNAs (miRs) are a new and relatively understudied class of genes that are known as non-coding because they are not used by cells for the direct synthesis of proteins. Since only about 1.5% of the human genome encodes for proteins, there is a large expanse of understudied non-coding genetic elements, including miRs, that could hold a wealth of information about the factors that influence prostate cancer development and progression. Dr. Shawn Lupold, an FY07 PCRP New Investigator Award recipient, and his research team at the Johns Hopkins University have undertaken this challenge to focus on certain miRs to determine if they could cause prostate cancers to develop into aggressive phenotypes such as CRPC, which continues growing even after deprivation from androgen hormones. They found that one such miR, miR-21, was capable of driving tumors to grow after castration.

miR-21 was one of 15 miRs that were discovered in prostate cancer cells by analyzing the changes in miR expression levels after treatment with androgens using a high-throughput microarray assay. The discovery that the transcription of this one specific miR was directly induced by the activated AR was particularly important because the AR remains active in many cancers, even after castration therapy. Dr. Lupold’s team also showed that over-expression of miR-21 in castration-sensitive prostate cancer cells and tumors caused faster cell and tumor growth and, even more importantly, elevated expression of miR-21 alone was found to be sufficient to cause these castration-sensitive tumors to become castration-resistant.

miR-21 shows promise for clinical application, as preliminary studies from several groups suggest that miR-21 levels are higher in the tissue or serum of some patients with more aggressive prostate cancer. Other miRs have also been observed to be over- or under-expressed in the tissues and serum of men with more aggressive prostate cancer. While larger studies are still needed to validate the use of miR expression in distinguishing aggressive from indolent prostate cancer, Dr. Lupold’s work shows that these non-coding elements can contribute to aggressive prostate cancer biology, which suggests that their detection may be useful for improving prognostics for managing prostate cancer. Moreover, these non-coding RNAs may be targets for cancer therapeutics.
Discovery of a Single Genetic Mutation in Castration-Resistant Prostate Cancer Could Lead to New Biomarkers and Targeted Therapies

Nima Sharifi, M.D., Cleveland Clinic Foundation

The growth of prostate cancer is fueled by increased androgen synthesis within cells via a mechanism of sustained AR signaling. Activated by androgens such as dihydrotestosterone (DHT), the AR signaling pathway has served as a fundamental target of recent FDA-approved drugs for prostate cancer treatment, like abiraterone. Unfortunately, prolonged therapy with androgen synthesis inhibitors can result in drug resistance and the development of CRPC. Abiraterone can limit the growth of CRPC, but the presence of residual amounts of a key steroid precursor, dehydroepiandrosterone (DHEA), allows for continued production of the AR-activating androgen DHT, promoting abiraterone resistance in CRPC.

The mechanisms that enhance DHT production from DHEA and promote abiraterone resistance in CRPC remain poorly understood. With this in mind, and with support from an FY08 Physician Training Award, Dr. Nima Sharifi and his multidisciplinary team of researchers at the University of Texas Southwestern Medical Center discovered a mutant version of the 3β hydroxysteroid dehydrogenase type 1 enzyme (3βHSD1), that was present in a subset of CRPCs. This mutation, N367T, prevents the enzyme from being ubiquitinated, a key part of the degradation process. By blocking ubiquitination, the 3βHSD1 is not degraded, and remains present in cancer cells much longer than the wild-type version.

The sustained presence of the mutant 3βHSD1 enzyme is significant since it in turn activates one of the rate-limiting steps in the androgen synthesis pathway – the conversion of DHEA to androstenedione (AD). By allowing for continued activation of this rate-limiting step, the 367T promotes androgen production and ultimately the growth of CRPC. The discovery of 367T and its role in the androgen synthesis pathway suggests that inhibition of this steroidogenic enzyme may limit prostate cancer. Dr. Sharifi and his team, now located at the Cleveland Clinic Foundation, are working towards the identification of a small molecular inhibitor of this enzyme that may be used for prostate cancer therapy. The added potential for using the N367T mutation as a biomarker for CRPC further emphasizes the significance of this finding and its potential impact on prostate cancer patients.

Polycomb Gene BMI1 as a Promising Target in Prostate Cancer Chemoresistance

Dr. Mohammad Saleem (Bhat), Ph.D., The Hormel Institute, University of Minnesota

CRPC is a hard-to-treat disease, and little is known about the reasons contributing to this form of prostate cancer. Thus, identification of one or more critical molecules involved in conferring chemoresistance would be an important advancement in developing new ways to prevent or treat this deadly form of the disease. Genes that regulate various cellular processes, such as the cell cycle and programmed cell death (apoptosis), could be involved in the development of chemoresistance and the increased invasiveness of prostate cancer cells. One such group is the polycomb group of genes, which has been associated with several types of cancer including prostate cancer. The emergence of a specific member of the polycomb family, BMI1, as a gene with involvement in stem-cell renewal makes it an attractive target for further investigation.

Dr. Mohammed Saleem Bhat, recipient of an FY07 New Investigator Award from the DoD PCRP, along with his research team at the Hormel Institute, University of Minnesota, has provided compelling evidence that BMI1 plays a crucial role in determining the fate of tumors treated with chemotherapy. By employing a number of assays such as microarray, ChIP, immunoblot, and Luciferase reporter assays, they identified a unique mechanism through which BMI1 rescues tumor cells from chemotherapy by regulating the activity and binding of the TCF4 transcription factor to the control region of BCL2, an anti-apoptotic gene. They also noticed that BMI1 is capable of driving normal cells to an overactive growth state by breaking their normal process of aging and death (senescence), suggesting that BMI1 might play a critical role in breaking the sleeping mode of tumor cells and driving them towards proliferation. The fact that BMI1 expression is not influenced by androgen, which is the target of most chemotherapy treatments, further suggests that BMI1 might play a role in driving indolent disease to a more aggressive, androgen-independent disease state.

Dr. Bhat’s group also tested the ability of BMI1 blockade to enhance the results of docetaxel treatment. Using a mouse xenograft model, they showed that targeting BMI1 in chemoresistant cells sensitizes them to docetaxel therapy, and that the success of docetaxel therapy in the xenograft mouse model was highly dependent on the level of BMI1. This suggests that targeting BMI1 should be a part of therapeutic strategy to combat chemoresistant cancer, and that BMI1 interventions may provide opportunities to enhance the efficacy of chemotherapy in a large group of prostate cancer patients.
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

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 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 to that patient.

Recent 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 (ZYTI®) 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
Opportunities for Resolving Prostate Cancer Health Disparities

North Carolina-Louisiana Prostate Cancer Project

The PCaP was launched in 2002, when the PCRP awarded Dr. James Mohler funding to initiate one of the largest investigations ever to explore racial differences affecting prostate cancer aggressiveness. The goal was to delineate the factors that contribute to the high incidence and disproportionate rate of prostate cancer morbidity and mortality in African American versus Caucasian men. The project, a collaboration between the University of North Carolina at Chapel Hill, the Louisiana State University Health Sciences Center, and the Roswell Park Cancer Institute, studied 1,130 African American and 1,128 Caucasian men newly diagnosed with prostate cancer in North Carolina and Louisiana. The men were evaluated by health professionals using information gathered from questionnaires, medical records, and biological specimens provided by each study participant. Today, the data and resources from the PCaP project continue to be updated with new clinical follow-up information and remain available to the prostate cancer research community in the PCaP central database (http://ncla-pcap.org/). These resources continue to be used to fuel new studies regarding the biologic and socio-cultural factors underlying the disproportionate incidence and death rate from prostate cancer among African American men.

Providing Critical Tissue Samples to Help Drive Prostate Cancer Research

Prostate Cancer Biorepository Network

In 2009, the PCRP launched the PCBN in response to the prostate cancer research community’s need for high-quality, well-annotated human prostate cancer biospecimens. This consortium was tasked with collecting biospecimens and fostering an infrastructure to facilitate biomarker studies. The PCBN started as a collaboration between two institutions – The Johns Hopkins School of Medicine (Hopkins) and the New York University Medical Center with the coordinating center located at Hopkins. Two additional sites have since been added: the University of Washington and Memorial Sloan Kettering Cancer Center. Both institutions provide a rich resource of scientific expertise and biospecimens to assist the research community in its efforts to incorporate biospecimens into research projects. Hopkins serves as the coordinating center and provides administrative, operational, and data management services. The PCBN’s website (http://prostatebiorepository.org) offers a wealth of information including how to request biospecimens and/or data, application forms, review criteria for requests, and much more.
PCRP FY12 and FY13 Investments

In FY12, based on the significant investment the program had made in discovery-driven research over the previous 15 years, new award mechanisms were developed to encourage large-scale, team-based translational and clinical research that would transform clinical practice. In FY13, the strategic recommendation was made to extend key support for research resources by again offering the Clinical Consortium Award and the Prostate Cancer Pathology Resource Network Award, both of which are designed to increase the pace of research by, respectively, leveraging resources in the conduct of prostate cancer clinical trials and providing high-quality human prostate cancer biospecimens to the research community. In addition, the program renewed its support for population science research in order to identify and investigate key determinants that affect prostate cancer patients. In both FY12 and FY13, the program continued its support of new discoveries, training for early-career investigators, and targeted efforts to understand and resolve disparities in prostate cancer incidence, morbidity, and mortality.

Table 1. PCRP Investment Summary for FY12 and FY13

<table>
<thead>
<tr>
<th>Focus and Award Mechanisms</th>
<th>FY12 Applications Received</th>
<th>FY12 Awards</th>
<th>FY13 Applications Received</th>
<th>FY13 Awards</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Impact Research</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biomarker Development Award</td>
<td>13</td>
<td>0</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Clinical Exploration Award</td>
<td>18</td>
<td>1</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Health Disparity Research Award</td>
<td>43</td>
<td>6</td>
<td>39</td>
<td>5</td>
</tr>
<tr>
<td>Laboratory – Clinical Transition Award</td>
<td>23</td>
<td>2</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Population-Based Impact Award</td>
<td>N/A</td>
<td>N/A</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Transformative Impact Award</td>
<td>10</td>
<td>3</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td><strong>Innovative Research</strong></td>
<td>387</td>
<td>31</td>
<td>387</td>
<td>20</td>
</tr>
<tr>
<td>Exploration – Hypothesis Development Award</td>
<td>338</td>
<td>32</td>
<td>322</td>
<td>38</td>
</tr>
<tr>
<td>Idea Development Award</td>
<td>144</td>
<td>13</td>
<td>87</td>
<td>14</td>
</tr>
<tr>
<td><strong>Training/Recruitment</strong></td>
<td>9</td>
<td>5</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Collaborative Undergraduate HBCU Student Summer Training Program</td>
<td>20</td>
<td>5</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Postdoctoral Training Award</td>
<td>122</td>
<td>31</td>
<td>104</td>
<td>22</td>
</tr>
<tr>
<td>Research Resources</td>
<td>N/A</td>
<td>N/A</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Clinical Consortium Award</td>
<td>N/A</td>
<td>N/A</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Prostate Cancer Pathology Resource Network Award</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1127</td>
<td>129</td>
<td>1029</td>
<td>121</td>
</tr>
</tbody>
</table>

N/A – Not offered that fiscal year
The Vision for FY14

The PCRP received $80M in FY14 congressional appropriations. The Integration Panel met to discuss the state of the science and to identify critical gaps in research. With advances in diagnosis and treatment extending lives, survivorship has become increasingly important to men living with prostate cancer. The program added a new overarching challenge to encourage investigators to develop strategies to optimize the physical and mental health of these men. Understanding the mechanisms of treatment resistance so that new or improved treatments can be developed was identified as another area of critical importance. The program re-offered the Clinical Exploration Award to fund early-phase clinical trials addressing this issue. The program also renewed its support for the PCBN by offering the Prostate Cancer Biospecimen Resource Site Award. This award will fund an additional site to help increase the acquisition of rare, high-quality, well-annotated biospecimens that are much needed by the research community. The following 12 award mechanisms were selected to maximize the impact of the FY14 PCRP investment towards eliminating death from prostate cancer and enhancing the well-being of men experiencing the impact of the disease.

Table 2. PCRP FY14 Vision (Award Mechanisms)

<table>
<thead>
<tr>
<th>Focus</th>
<th>Award Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impact Research</td>
<td><strong>Biomarker Development Award</strong>: Supports high-impact research aimed at analytical validation or qualification of known prostate cancer biomarkers or biomarker assays for rapid transfer to clinical practice.</td>
</tr>
<tr>
<td>Health Disparity Research</td>
<td><strong>Health Disparity Research Award</strong>: Supports high-impact approaches to prostate cancer health disparity research that represent new ideas. Additional funding available for the Qualified Collaborator and/or Nested Traineeship Options.</td>
</tr>
<tr>
<td>Laboratory–Clinical Transition</td>
<td><strong>Laboratory–Clinical Transition Award</strong>: Provides funding for product-driven preclinical studies of promising novel lead agents or medical devices that may revolutionize prostate cancer clinical care.</td>
</tr>
<tr>
<td>Population Science Impact</td>
<td><strong>Population Science Impact Award</strong>: Supports high-impact, population science approaches to prostate cancer research with emphasis on biomarkers, especially those relevant to aggressive disease; genetics/genomics; therapy and predictors of response or resistance; and survivorship and palliative care.</td>
</tr>
<tr>
<td>Innovative Research</td>
<td><strong>Clinical Exploration Award</strong>: Supports rapid execution of hypothesis-based, early-phase clinical trials to test interventions that will have a major impact on prostate cancer management.</td>
</tr>
<tr>
<td>Exploration–Hypothesis Development</td>
<td><strong>Exploration–Hypothesis Development Award</strong>: Supports highly innovative, untested, potentially groundbreaking concepts in prostate cancer.</td>
</tr>
<tr>
<td>Idea Development</td>
<td><strong>Idea Development Award</strong>: Supports new ideas that represent innovative, high-risk/high-gain approaches to prostate cancer research. The New Investigator Option provides additional emphasis for investigators in the early stages of, or developing, independent prostate cancer research careers.</td>
</tr>
<tr>
<td>Synergistic Idea Development</td>
<td><strong>Synergistic Idea Development Award</strong>: Supports new or existing partnerships between two or three independent investigators to address a central question in prostate cancer through synergistic and innovative approaches that may include high risk with potential for significant impact.</td>
</tr>
<tr>
<td>Training/Recruitment</td>
<td><strong>Collaborative Undergraduate HBCU Student Summer Training Program Award</strong>: Supports new or existing summer training programs for undergraduate HBCU students at host institutions with thriving prostate cancer research programs.</td>
</tr>
<tr>
<td>Physician Research Training</td>
<td><strong>Physician Research Training Award</strong>: Provides support for physicians with clinical duties to pursue training for careers at the forefront of prostate cancer research.</td>
</tr>
<tr>
<td>Postdoctoral Training</td>
<td><strong>Postdoctoral Training Award</strong>: Provides support for recent doctoral graduates to pursue postdoctoral training in prostate cancer research.</td>
</tr>
<tr>
<td>Research Resources</td>
<td><strong>Prostate Cancer Biospecimen Resource Site Award (New for FY14)</strong>: Provides support for infrastructure that will facilitate participation in an existing PCRP-funded prostate cancer biorepository network through the collection, processing, annotation, storage, and distribution of high-quality human biospecimens.</td>
</tr>
</tbody>
</table>
For more information, visit
http://cdmrp.army.mil
or contact us at:
usarmy.detrick.medcom-cdmrp.mbx.cdmrp-public-affairs@mail.mil
(301) 619-7071