CDMRP
Department of Defense
Prostate Cancer Research Program

PCRP erspectives

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In This Issue

The PCRP Recognizes Prostate Cancer Awareness Month

Prostate cancer is the most commonly diagnosed cancer in men and will occur in nearly one in six men within their lifetime.

Current estimates show that in 2009 alone, 192,280 men will be diagnosed with prostate cancer, and 27,360 men will die from the disease[1]. In recognition of this serious health threat, many health organizations have raised awareness of this disease by promoting a Prostate Cancer Awareness Month in their region. In 2001, this effort was nationalized with Senate Resolution 138 and Presidential Proclamation 7492, which formally declared September to be National Prostate Cancer Awareness Month.

In recognition of Prostate Cancer Awareness Month, the Prostate Cancer Research Program (PCRP) is initiating this ***PCRP Perspectives*** newsletter to inform the prostate cancer survivor and research communities about the program's efforts to conquer this disease. The PCRP, administered by the Department of Defense, was established in 1997 by an initial congressional appropriation of $45 million (M). Grassroots efforts led by the prostate cancer advocacy community resulted in the initial congressional

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Targeted Therapies:

PCRP Investigators Advancing Treatment to Conquer Prostate Cancer

Due in part to the growing awareness of prostate cancer as a threat to men's health, early detection is rising in the United States, corresponding to a decreasing mortality rate. For men newly diagnosed with localized disease, a range of treatment options is available, such as "watchful waiting," radiation therapy, or the surgical removal of the prostate (prostatectomy), depending on the stage of cancer. Despite this encouraging news, some men will experience disease recurrence, treatment for which may include radiation, chemotherapy, or androgen deprivation therapy (ADT). ADT is highly effective for different periods of time, but eventually prostate cancer cells become resistant to this therapy and metastasize to other tissues, particularly to bone. There is currently no cure for ADT-resistant, metastatic prostate cancer so there is a great need for new and effective treatment strategies.

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Featured Opinion

Donald J. Tindall, Ph.D., Professor, Director and Vice Chair of Urologic Research, Carl Rosen Professorship in Urology, Departments of Urology, Biochemistry, Molecular Biology, Mayo Clinic College of Medicine

Fiscal Year 2010 Chair of the PCRP Integration Panel

This year, the Prostate Cancer Research Program will re-emphasize its vision to "conquer prostate cancer" and its mission to "fund research that will eliminate prostate cancer." The efforts of the PCRP toward conquering prostate cancer will be driven by congressional appropriations in fiscal year 2010 (FY10). The theme of our featured article "Targeted Therapies" is especially germane to both our vision and mission statements.

The current landscape of targeted therapies in prostate cancer is especially propitious. Recent advances, which have been funded largely by the PCRP, have identified cellular mechanisms that contribute to the etiology and progression of prostate cancer. Many of these discoveries were based on the hypothesis that the androgen receptor is critical for the viability of prostate cancer cells both before and after androgen ablation therapy, which is a cornerstone therapeutic intervention for advanced prostate cancer. New, more powerful antagonists of the androgen receptor have recently been developed. Also, discovery of novel androgen receptor

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VISION: Conquer prostate cancer.
MISSION: Fund research that will eliminate prostate cancer.

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PCRP-funded investigators have risen to this challenge by using groundbreaking approaches—some of which are already being tested in early phase clinical trials—to therapeutic development for advanced disease, designing therapies that will be both effective in ADT-resistant disease and not harmful to healthy tissues. These approaches include the use of plant toxins, enzymes, cell surface proteins, glycoproteins, peptides, and hormone receptors as targeting mechanisms that direct therapeutics to prostate cancer tissues while avoiding damage to healthy tissue.

Prostate-specific membrane antigen (PSMA) is a cell surface protein that is expressed at high levels in the vasculature of prostate cancer and many other solid tumor types at all stages of the disease, making it a key target for therapy. PCRP investigators are taking advantage of the biological activities and unique patterns of expression of PSMA and other similar molecules by developing varied strategies to deliver targeted therapy. For example, harnessing molecule and tissue specificity is a crucial part of the highly potent therapy being developed by Johns Hopkins University (JHU) researcher **Dr. Samuel Denmeade** (pictured left), a recipient of FY01 and FY06 Idea Development Awards. Dr. Denmeade has taken advantage of the toxic properties of thapsigargin (TG), a plant toxin that kills all cells independent of proliferation rate and tissue type. TG does this by blocking the sarco(endo) plasmic reticulum Ca++ ATPase (SERCA) pump from transporting calcium across the sarco(endo)plasmic reticulum membrane. Given its universal effect, the toxin must first be rendered safe for healthy tissues.

To accomplish this task, Dr. Denmeade synthesized inactive analogs (prodrugs) of TG and attached them to a specific peptide carrier, chosen because it also serves as a substrate for PSMA. Only in the presence of PSMA, the cytotoxin was released from the prodrug into the local environment. The prodrugs were stable and exhibited 15- to 57-fold higher toxicity to prostate cancer cells than normal cells. One lead prodrug demonstrated complete and sustained inhibition of prostate cancer tumor growth with minimal toxicity to healthy tissue (Figure 1).

Another mechanism for therapeutic specificity was developed by **Dr. Ming Zhao** at Anticancer, Incorporated, whose effort was funded by an FY05 Idea Development Award. A virulent strain of the *Salmonella typhimurium* bacterium was engineered to target and kill metastatic prostate cancer cells in mice. This strain, A1-R, grows selectively in low oxygen and dying regions of tumors without affecting healthy tissue. Target specificity was confirmed by using A1-R bacteria expressing green fluorescent protein (GFP). To measure efficacy, mice with PC-3 cell line-derived prostate tumors were given weekly injections of A1-R. Strong antitumor activity was observed in the treated mice, which had 75% smaller tumors after 30 days compared with untreated mice. In addition, 40% of the treated mice appeared to be completely cured of the prostate tumor with no recurrence after treatment stopped.

At the University of Rhode Island, **Dr. Yana Reshetnyak**, funded by an FY05 New Investigator Award, engineered a novel strategy for the selective targeting of prostate cancer cells by making use of their unique properties. Cancer cells maintain lower extracellular pH than normal cells due to lactic acid production and elevated CO2 levels. Dr. Reshetnyak created a 36-amino acid peptide, derived from bacteriorhodopsin, called pH Low Insertion Peptide (pHLIP), which acts as a microscopic molecular syringe to selectively deliver therapeutic agents into cancer cells. This technique injects phalloidin, a mushroom toxin coupled to pHLIP, into cells at acidic pH, thereby selectively targeting cancer cells. In vitro testing demonstrated that pHLIP prevents uptake of the toxin in normal liver cells, showing promise that this therapy may have only minimal side effects. Since pHLIP can be attached to toxins or other molecules that are fluorescent or radiolabeled, it can also serve as a specific and efficient imaging tool.

New approaches in molecular targeting are also being applied to imaging, which can be a powerful tool in prostate cancer detection, diagnosis, and treatment, and

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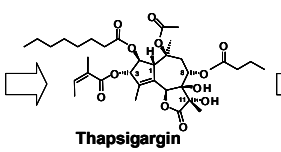
Did You Know...

- Prostate cancer is the **second leading cause of cancer deaths** among men in the United States after lung cancer.
- The PCRP is the **second largest funding** organization for prostate cancer research after the National Institutes of Health.
- More than **1,200 applications** for PCRP funding are received each year from prostate cancer researchers across the United States and around the world.
- On average, more than **60 prostate cancer survivors** participate in PCRP peer review each year.

Thapsia garganica



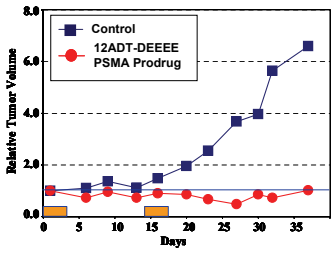


Figure 1. Thapsigargin is isolated from the seeds of Thapsia garganica and is converted to a prodrug by coupling to the PSMA-specific peptide Asp-Glu-Glu-Glu-Glu (DEEEE). Prodrug treatment of PSMA-producing prostate cancer xenografts results in regression and sustained growth inhibition.

Prostate Cancer Research Program

For more information:
http://cdmrp.army.mil/pcrp/default

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In This Issue

Consumer Spotlight

Survivors Impacting Research to Help Find a Cure

I am Manny Vazquez, a 13-year prostate cancer survivor. I owe my life to my wife, who nagged me for a long time to get a regular medical checkup. When I finally acquiesced, I learned that I had two very serious problems: polyps in the colon turning into cancer and a higher than normal PSA reading, later diagnosed as very aggressive prostate cancer. Both problems were addressed with the removal of the polyps and a subsequent radical prostatectomy, which changed the course of my life. I have since learned the value of preventive medicine in the form of regular annual checkups.

I would have not been able to coast toward the road to recovery without Tex Us TOO, my prostate cancer support group in Houston, Texas. From this group I received much and, in turn, I became empowered to give back. I have reached perhaps thousands of individuals, communicating in both English and Spanish, through presentations at churches, schools, civic organizations, corporate health fairs, and radio and television segments, and also as a monthly newsletter editor and contributor to a published book, *Prostate Cancer: Portraits of Empowerment*[1]. Our mission is to provide information and support although we do not offer medical advice. Medical professionals, with their vast knowledge and treatments, care very effectively for a diseased organ or gland, but they may not be able to fathom entirely the internal struggles their patients wage confronting their disease—during or after treatment—unless they are cancer patients themselves.

One of the most rewarding experiences in my life has been my participation as a consumer reviewer in the Department of Defense PCRP, managed by the Office of the Congressionally Directed Medical Research Programs. I never thought that I would be working alongside some of the brightest researchers in the field evaluating scientific research projects in a peer review setting. The unique perspective that I, as a prostate cancer survivor and community advocate, offered during peer review provided a frame of reference that the scientists and clinicians would not have considered otherwise during these deliberations. My views were reflected in the final outcome of the peer review process, which made the experience deeply gratifying for me.

As I consider myself a "professional survivor," I believe my cumulative experiences can be valuable to help the newly diagnosed, or those like me, with quality-of-life issues related to therapies. In the 13 years since my diagnosis, the depth and breadth of prostate cancer research have advanced exponentially. I am extremely hopeful about the breakthroughs that lay ahead as the PCRP continues to move forward toward finding a cure for prostate cancer.

[1]Jelsing N. 1999. Prostate Cancer: Portraits of Empowerment. *Westview Press, Boulder, Colorado.*

Calendar of Events

SEPTEMBER

12–13: Annual Prostate Cancer Conference, "Making a Positive Impact on Quality of Life," Los Angeles, California. Sponsored by the Prostate Cancer Research Institute.

13–16: American Association for Cancer Research (AACR) Metabolism and Cancer Conference, La Jolla, California.

23–24: The 10th Annual Summit to End Prostate Cancer, Washington, DC. Sponsored by Zero – The Project to End Prostate Cancer.

24–25: Fifth Annual African American Prostate Cancer Disparity Summit, Washington, DC. Sponsored by the Prostate Health Education Network.

OCTOBER

8–11: AACR Frontiers in Basic Cancer Research, Boston, Massachusetts.

20–24: Fifth International Conference on Tumor Microenvironment: Progression, Therapy, and Prevention, Versailles, France. Sponsored by the AACR and the Institut National du Cancer.

NOVEMBER

5–8: SBUR/ESUR Eighth World Congress in Urological Research, "Molecular Targets for Diagnostics & Therapeutics in Urology," New Orleans, Louisiana. (Be sure to attend the PCRP presentation in the "Training with the Experts Workshop.")

15–19: AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics, Boston, Massachusetts.

DECEMBER

6–9: AACR Frontiers in Cancer Prevention Research, Houston, Texas.

Program News

- A new preproposal process for Idea Development and Synergistic Idea Development Awards was initiated in FY09 and is currently under evaluation.
- The PCRP received 849 applications for FY09 funding.
- Peer review for most award mechanisms was completed in July 2009. Also, 575 scientist reviewers and 44 consumer reviewers participated in PCRP peer review.
- The inaugural issue of *PCRP Perspectives* was published in September 2009!
- Programmatic review for most award mechanisms will be conducted in October 2009 and funding status notifications provided in early November.
- Vision setting for FY10 will be conducted in November 2009.

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in helping to understand the mechanisms underlying prostate cancer development and progression to metastasis. Funded by an FY05 Idea Development Award, **Dr. Martin Pomper** has utilized PSMA's specificity to prostate cancer cells in an effort to improve imaging of prostate cancer tumors. In his laboratory at JHU, he developed several radiolabeled small-molecule ligands with high affinity to PSMA (Figure 2). These molecules promote rapid entry into tumors and facilitate detection through the use of positron emission tomography (PET). One compound, [18F]DCFBC, was found to have a particularly high signal-to-noise ratio and is patented through a pharmaceutical company for further development. Derivatives of this compound are in Phase I/II clinical trials to test for safety and efficacy in prostate cancer patients.

While these examples represent only a small sampling of the targeted therapeutic studies that are being conducted by PCRP investigators, it is clear that novel therapeutic strategies in prostate cancer are being sought to address the failure of chemotherapeutic agents in some patients, and especially in metastatic disease. Using innovative approaches such as these will also lead to therapies that can be tailored to each individual patient's needs and therefore be most effective. As these new treatment modalities are moved from the laboratory to clinical trials, there is hope that a breakthrough in prostate cancer therapy is on the near horizon and will offer prostate cancer patients better options for treatment, survival, and quality of life.

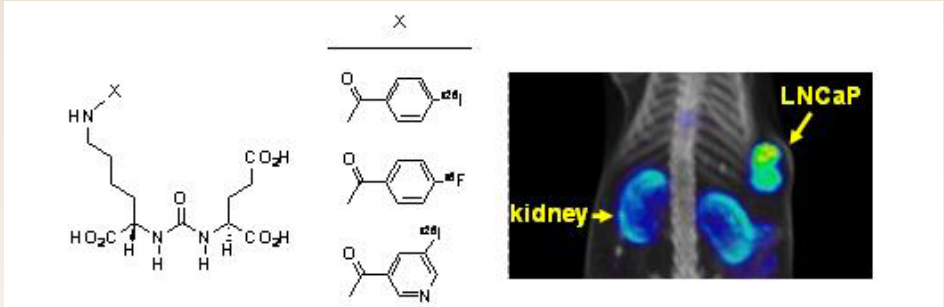

Figure 2. Imaging agents of the urea series that bind specifically to the PSMA

From Chen, Y. et al. Radiohalogenated PSMA-based ureas as imaging agents for prostate cancer. *J Med Chem.* 2008; 51:7933-7943.

References

Reshetnyak YK, Andreev O, Segala M, et al. 2008. Energetics of peptide (pH-LIP) binding to and folding across a lipid bilayer membrane. *Proc Natl Acad Sci U S A.* 105(40):15340-15345.

Zoonens MA, Reshetnyak YK, and Engelman DM. 2008. Bilayer interactions of pHLIP, a peptide that can deliver drugs and target tumors. *Biophys J.* 95;225-235.

Mease RC, Dusich CL, Foss CA, et al. 2008 N-[N-[(S)-1,3-dicarboxypropyl] carbamoyl]-4-[18F]fluorobenzyl-L-cysteine, [18F]DCFBC: A new imaging probe for prostate cancer. *Clin Cancer Res.* 14:3036-43.

Zhao M, Geller J, Ma H, et al. 2007. Monotherapy with a tumor-targeting mutant of *Salmonella typhimurium* cures orthotopic metastatic mouse models of human prostate cancer. *Proc Natl Acad Sci U S A.* 104:10170-10174.

Mease RC, Dusich CA, Foss CA, et al. 2006. Synthesis of N-[N-[(S)-1,3- dicarboxypropyl]carbamoyl]-[18F]fluorobenzyl-L-cysteine, [18F]DCFBC, its biodistribution and use in imaging prostate cancer xenografts. Presented at the 53rd Annual Meeting of the Society of Nuclear Medicine, San Diego, California.

» AWARENESS, CONTINUED FROM PG. 1

appropriation, and since then, the PCRP has received a total of $970M from Congress to promote innovative, high-risk/high-impact research aimed at the prevention, detection, diagnosis, and/or treatment of human prostate cancer. The program supports both individual investigators and multidisciplinary team science using a variety of award mechanisms that encompass basic, translational, and clinical research and emphasize prostate cancer health disparities research.

A hallmark of the PCRP is the partnership of consumer advocates with scientists and clinicians who participate in peer and programmatic reviews and in setting program priorities. Consumer advocates' unique experiences with prostate cancer help scientists understand the human side of the disease and, therefore, facilitate funding recommendations that reflect the needs of patients and their families, as well as the research community. Examples of some of the PCRP's outstanding funded research are highlighted in this issue of ***PCRP Perspectives***. PCRP investigators are making major advances in the fight against prostate cancer by developing new, targeted therapies aimed at improving detection and diagnosis, assessing treatment and efficacy, and providing improved delivery of targeted therapy. These breakthroughs are just a few of the several hundred studies that are currently supported by the PCRP. Going forward, the PCRP will continue to prime its pipeline with innovative and impactful studies that will provide solutions to improve methods of prevention, early detection, treatment, and quality of care to achieve its vision of conquering prostate cancer.

[1] Source - *Cancer Facts and Figures* 2009, American Cancer Society

Summary of FY08 PCRP Award Data

Research Awards

Clinical Consortium 13 Awards

Clinical Trial 2 Awards

Health Disparity Research 9 Awards

Idea Development 50 Awards

Laboratory-Clinical Transition: Stage I 3 Awards

New Investigator 25 Awards

Synergistic Idea Development 10 Awards

Training/Recruitment Awards

Collaborative Undergraduate HBCU Student Summer Training 8 Awards

Health Disparity Training 3 Awards

Physician Research Training 7 Awards

Prostate Cancer Training 48 Awards

TOTAL 178 Awards

» OPINION, CONTINUED FROM PG. 1

variants emphasizes the importance of the androgen receptor in castration-resistant prostate cancer. Moreover, the essential role of androgen metabolism in prostate cancer initiation and progression has been underscored by two important clinical trials. Both Dutasteride and Abiraterone, which inhibit metabolism of androgens, showed promising results in clinical trials with prostate cancer patients. Recurrent fusions of androgen-regulated genes with members of the ETS family of oncogenes have been identified in a majority of prostate tumors, suggesting a role in cancer initiation. Thus, these significant discoveries have paved the way for new targets for therapeutic intervention.

For FY09, the PCRP will be funding a number of award mechanisms that should greatly facilitate research in targeted therapies. These include Idea Development, Population-Based Idea Development, Synergistic Idea Development, New Investigator, and Physician Research Training Awards. These awards are designed to support innovative approaches to prostate cancer research. Also, Prostate Cancer Pathology Resource Network Awards will support the development of a consortium infrastructure that will facilitate prostate cancer research. Health Disparity Research, Health Disparity Training, and Collaborative Undergraduate Historically Black Colleges and Universities (HBCU) Student Summer Training Program Awards will support prostate cancer health disparity-focused projects by investigators at multiple points in their careers. Finally, Prostate Cancer Training Awards will support prostate cancer research training for individuals in the early stages of their careers. Supporting young investigators has been a hallmark of the PCRP. Thus, we look forward to a productive year that will advance the war on prostate cancer to the betterment of mankind.

Grant Writing Tips

- Read the Program Announcement carefully!
  - Ensure that you have included all required components and have adhered to all page limitations.
- Find readers for your proposal, even in the early draft stage.
  - Ensure that your ideas are expressed clearly and that the formatting, spelling, and grammar show careful preparation.
- Be sure to describe alternative strategies to overcome potential problems in the project.
  - Few, if any, research strategies are perfect from the start, but reviewers will judge a project's feasibility in part by how much the Principal Investigator has considered how to overcome research roadblocks.

Watch for more tips in the next issue!

Visit the PCRP Webpage for Up-to-date Program Information

The DOD Prostate Cancer Research Program (PCRP) supports innovative ideas and technologies to accelerate our vision to conquer prostate cancer through individual, multidisciplinary, and collaborative research. These efforts are focused toward basic research discoveries and translating discoveries into clinical practice to improve the quality of care and life of men with prostate cancer. For more information on PCRP initiatives, highlights of funded research, and consumer profiles, please visit the PCRP webpage at

http://cdmrp.army.mil/pcrp/default

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