



CDMRP



Department of Defense

Prostate Cancer Research Program (PCRP)

PCRP Perspectives

Volume 4, Number 2 – October 2014

In This Issue

page 1 Featured Opinion; New Agents; Funded Investigators **page 2** Funded Investigators continued **page 3** Spotlight; Calendar of Events; Contact Info
page 4 New Agents continued; Did You Know **page 5** Funded Investigators continued; Program News
page 6 Featured Opinion continued; Grant Writing Tips

Featured Opinion

AR “Identity Crisis” in Prostate Tumors Helps Therapeutic Targeting in Patients



*Natasha Kyprianou, M.D., Ph.D.
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Chair in Urology Research
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Compelling findings accumulating at a rapid pace have enhanced our understanding of the relationship

between the emergence of genetic changes in the androgen receptor (AR), treatment failure, and clinical progression of prostate cancer in patients on antiandrogen treatment. Almost all prostate cancer patients with metastatic disease respond to androgen deprivation induced by first-generation antiandrogens (via induction of tumor cell death), but they invariably relapse and are ultimately confronted with the emergence of castration-resistant prostate cancer (CRPC). Thus, a long-standing challenge has been to overcome this therapeutic resistance and prostate tumor progression to lethal disease.

What we have learned through seminal work by Charles Sawyers, Steven Balk, and Jun Luo, and others supported by the Department of Defense PCRP, is that the AR remains the critical driver of therapeutic response and resistance in patients with metastatic CRPC. We

» continued, **SEE OPINION, PG. 6**

New Agents in Prostate Cancer: Unprecedented Success and More Work to be Done

Tomasz M. Beer, M.D., Knight Cancer Institute, Oregon Health & Science University

With the publication of the PREVAIL trial in June of 2014, the first chapter of a new era in advanced prostate cancer therapy was successfully completed. Four global clinical trials – that had much in common – all yielded positive results and changed clinical practice standards (see table on page 4). All four were published in the *New England Journal of Medicine*, beginning in 2011 and ending in 2014.

In many ways, our journey to this point is a remarkable story. The prostate gland fully matures only in the presence of testosterone. Clues that suggested a link between

hormones and prostate growth were first noticed as early as 1786 in deer and in moles. That castration reduces prostate size was confirmed in dogs in 1940 and, by 1942, the discovery that human prostate cancer responds to surgical castration was reported. This discovery launched a new era of hormonal therapy for advanced prostate cancer. Hormonal therapy provided high-quality and relatively long-lasting responses for most patients with advanced prostate cancer. But it was not a cure. Following the initial discoveries, a number of agents that manipulate the hormonal system were eventually developed. These

» continued, **SEE NEW AGENTS, PG. 4**

PCRP-Funded Investigators in Endocrinology Work toward Improving Prostate Cancer Treatment

A major challenge facing the prostate cancer community is the need to develop more effective treatments and address mechanisms of resistance for men with high-risk or metastatic prostate cancer. The driving force underlying the growth of prostate cancer stems from male hormones, also referred to as androgens. The primary male hormone, testosterone, is produced mainly by the testicles, while other weaker androgens are produced by the adrenal glands. Once taken up by prostate cancer cells, androgens

bind to the androgen receptor (AR), a protein that “turns on” genes that cause prostate cancer cells to grow and “turns off” genes that cause them to die. In 1941, Dr. Charles Huggins published his groundbreaking work showing that blocking androgen production slowed the progression of disease in men with metastatic prostate cancer. Since this finding, for which Dr. Huggins won the *1966 Nobel Prize in Physiology or Medicine*, androgen deprivation therapy (ADT) has been the cornerstone of advanced prostate

» continued, **SEE FUNDED INVESTIGATORS, PG. 2**

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.

» FUNDED INVESTIGATORS CONTINUED FROM PG. 1

cancer treatment. Reducing a patient's androgen levels, either through surgical or chemical castration, is initially a very effective treatment for advanced prostate cancer. Unfortunately, prostate cancer cells frequently become resistant to this therapy and the patient's disease is then referred to as "androgen-independent" or castration-resistant prostate cancer (CRPC). When this point is reached, the outlook is bleak due to a lack of treatment options.

The PCRP — in its effort to understand the cellular and molecular mechanisms of treatment resistance and to develop the next generation of therapies for men with high-risk or metastatic prostate cancer — has funded 189 research projects concerning hormone metabolism, hormone receptors, and hormone pathogenesis. The program has also provided substantial support in developing the **Prostate Cancer Clinical Trials Consortium (PCCTC)**. The PCRP partnered with the Prostate Cancer Foundation in 2005 to support this network of the nation's top clinical trial experts to accelerate the movement of new prostate cancer therapies through clinical testing to U.S. Food and Drug Administration (FDA) approval. The efforts of the PCCTC have contributed significantly to the most noteworthy advances in almost a decade in the treatment of metastatic CRPC: FDA approval of two new drugs, abiraterone and enzalutamide. Compared with previous anti-androgens, both abiraterone (ZYTIGA®), a CYP17A inhibitor that blocks androgen production, and enzalutamide (XTANDI®), a next-generation anti-androgen with increased affinity for AR, have significantly extended the survival rate for men with metastatic prostate cancer.

The wide availability of abiraterone and enzalutamide, and their superiority to older therapies at blocking androgen synthesis and AR signaling, respectively, provides hope for many men with advanced disease. But, similar to castration and the older ADT agents, resistance may still eventually occur. Indeed, the incentive to develop these new drugs came from a major paradigm-shifting revelation that even though the androgen levels circulating in the blood were low and nearly undetectable after castration or treatment with the older drugs, AR signaling remained high in the tumor cells due to the synthesis of androgens in the tumor. Since the PCRP's inception in 1997, the program's investigators have been working to develop a better understanding of this phenomenon. **Dr. Steven Balk**, of Beth Israel Deaconess Medical Center,

with support from the PCRP, discovered that one mechanism of this resistance to ADT was the increased production of enzymes, such as CYP17A1, within the tumor. These enzymes convert the weak androgens produced in the



Dr. Steven Balk

adrenal glands to potent androgens, for example, testosterone and dihydrotestosterone (DHT). Building on these findings, Dr. Balk teamed up with **Dr. Mary Ellen Taplin**, a PCCTC principal investigator at the Dana-Farber Cancer Center, and initiated a phase II clinical study to investigate the benefit of blocking several pathways of androgen synthesis. Men with CRPC were treated with a combination of the androgen synthesis inhibitors ketoconazole (CYP17A1 inhibitor) and dutasteride (SRD5A1/SRD5A2 inhibitor). The combination treatment markedly prolonged the time to tumor progression as compared with single-drug treatment, thus warranting further study of other combination therapies and mechanisms of relapse after ADT. With continued PCRP funding, Dr. Balk and collaborators are also focusing their efforts on understanding the specific molecular mechanisms of resistance to abiraterone and enzalutamide, as well as assessing therapeutic strategies for targeting these resistance mechanisms.

Dr. Nima Sharifi, at the Cleveland Clinic, also proposed to investigate mechanisms of androgen resistance, and during the course



Dr. Nima Sharifi

of his study, he discovered a gain-of-function mutation in CRPC tumors that accelerates intratumoral DHT synthesis, opening the floodgates for faster tumor growth. Since this mutation also

occurs naturally in the human population, Dr. Sharifi's work identified a biomarker and potential drug target for prostate cancer. Biomarkers and drug targets can sometimes exist in the most unlikely of biological pathways, and PCRP investigators found an intriguing link with circulating cholesterol.

Notably, PCRP awardees **Dr. Michael Freeman**, of Cedars-Sinai Medical Center, Los Angeles, and **Dr. Elahe Mostaghel**, of the Fred Hutchinson Cancer Research Center, showed that circulating levels of cholesterol in the blood correlate with intratumoral androgen levels and CYP17A expression levels, and can accelerate prostate cancer growth. Moreover, **Dr. Shafiq Khan**, of Clark Atlanta University, demonstrated that prostate cancer cells growing in laboratory dishes can synthesize testosterone directly from cholesterol and are not dependent on androgens. These findings suggest that cholesterol-lowering therapies (statins) may inhibit CRPC growth and synergize with therapies that target androgen synthesis and the AR.



Dr. Mary Ellen Taplin

The AR has developed many clever ways of circumventing scientists' efforts at blocking its pathway, including variation of the receptor itself. The AR is normally a modular protein consisting of an N-terminal region, a DNA binding domain, and an androgen (ligand) binding domain (LBD). However, in some CRPC tumors, the AR becomes altered and loses the LBD, thus allowing the tumor to grow and proliferate in the apparent absence of androgens. **Dr. Scott Dehm**, of the University of Minnesota, elucidated the genomic basis for these pathologic AR variants, showing that they are the result of DNA rearrangements in the AR gene and may serve as biomarkers for resistance to AR-targeting drugs (Figure 1) (e.g., bicalutamide and enzalutamide). **Dr. Yan Dong**, of Tulane University, also showed that AR variants



Dr. Scott Dehm

can interact with the normal full-length AR protein in an androgen-independent manner to drive prostate cancer growth in the absence of androgens, and reduce the ability of enzalutamide to inhibit normal AR. And with the help of critical samples from the PCRP **Prostate Cancer Biorepository Network**, **Dr. Jun Luo** of the Johns Hopkins University analyzed circulating tumor cells isolated from the blood of CRPC patients treated with enzalutamide or abiraterone. He detected



Dr. Yan Dong

» continued, **SEE FUNDED INVESTIGATORS, PG. 5**

In This Issue

Mark Kourey: A Personal Call to Action

My initial thought when I received my diagnosis 4 years ago was shock. It was completely unexpected; I was just 41. I was very thankful my primary physician ordered a PSA [Prostate-Specific Antigen] test “for good measure” when I had my annual



physical. My test results showed elevated PSA levels. I must commend my doctors and urologist for conducting the appropriate follow up, although each initially said “I’m sure it’s nothing, but let’s put you on the antibiotic.” Then it was, “I’m sure it’s nothing, but let’s do the biopsy.” My urologist was just as surprised as I was when the tests came back positive for prostate cancer.

Once the prostate cancer was confirmed, I immediately knew that this would be my personal call to action. I thought, “What do I do? How do I plan this out? I have to find everything I can about it.” I talked to a bunch of different doctors and got different opinions. I gathered all the data points I could possibly cram into my head. My friends thought it was funny that I kept track of my PSA ad nauseam on an excel spreadsheet. I also got my PSA taken at two different labs... because I knew they would have two different sets of data points.

As my PSA numbers were rising, I didn’t panic and go crazy; I just mentally slowed everything down. I realized my cancer was probably not going to grow too fast within a few months, which gave me time to research and better prepare. Again, it’s kind of the call to action; when all of these things converge, you make a decision as to what you’re going to do based on all the information you’ve gathered. Once you’ve made a choice on the treatment plan, it is really important to have no regrets for the decision.

My urologist also encouraged me to attend the prostate cancer support group Malecare. I had surgery and, as I went

through the healing process, I continued to go to Malecare on Wednesday nights. I wanted to help others who were newly diagnosed. I wanted to tell these men about what I went through and how I decided to handle my cancer, but that it may not be what you will go through. Each person has to figure out if they should get surgery, or get radiation, or decide to do nothing (“active surveillance”). I try to tell them, “Your head might be a mess right now, but take a breath and give yourself time to wrap your head around the matter, and have no regrets on any decision you make.” When someone in the group is newly diagnosed, I give them my phone number so that I can chat with them and walk them through. It’s all about helping others through their journey and their own call to action.

It was also through Malecare that I learned about the Prostate Cancer Research Program [PCRP] and the opportunity to represent my support group as a Consumer Reviewer. It has truly been an honor and a privilege to serve the PCRP. As a Consumer Reviewer, I am able to provide my honest and true feedback on the impact of potential research projects. I feel it is so important to put a face and a name to those of us whose lives — as well as the lives of our families and friends — continue to be affected by prostate cancer.

Additionally, I am so impressed by the fact that those of us affected by cancer are considered to have an equal voice on these review panels. I am equally impressed that the scientists on the review panels are truly interested in knowing what their research means to the prostate cancer survivors.

I hope that all of us together — through our own calls to action — are able to continue to make great strides in finding a cure, or at least in making this a long-term chronic disease with the least amount of disruption to our quality of life.

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

General questions:
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Application requirements:
Phone: (301) 682-5507
E-mail: help@cdmrp.org

Consumer involvement:
Phone: (301) 619-7071
E-mail: usarmy.detrick.medcom-cdmrp.mbx.cdmrp-public-affairs@mail.mil

Calendar of Events

October 2014						
Su	Mo	Tu	We	Th	Fr	Sa
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

12-15: 34th Congress of the Société Internationale d’Urologie, Glasgow, Scotland. Sponsor: Société Internationale d’Urologie

23-25: 21st Annual PCF Scientific Retreat, Carlsbad, CA. Sponsor: PCF

November 2014						
Su	Mo	Tu	We	Th	Fr	Sa
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2	3	4	5	6	7	8
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30						

5-8: 3rd Biennial Science of Global Prostate Cancer Disparities in Black Men Conference, Montego Bay, Jamaica. Sponsor: University of Florida Health Cancer Center/Prostate Cancer Transatlantic Consortium

9-12: AACR: The Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved, San Antonio, TX

18-21: AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, Barcelona, Spain. Sponsor: AACR/NCI/EORTC

December 2014						
Su	Mo	Tu	We	Th	Fr	Sa
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28	29	30	31			

6-7: AUA MR US Fusion Guided Prostate Biopsy: Beginner and Advanced Techniques, New York, NY. Sponsor: AUA

February 2015						
Su	Mo	Tu	We	Th	Fr	Sa
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
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5-7: 3rd Global Congress on Prostate Cancer, Rome, Italy. Sponsor: Astellas Pharma

11-14: Advancements in Urology 2015: An AUA/JUA Symposium, Honolulu, HI. Sponsor: AUA and JUA (Japanese Urological Association)

March 2015						
Su	Mo	Tu	We	Th	Fr	Sa
1	2	3	4	5	6	7
8	9	10	11	12	13	14
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29	30	31				

7-8: Joint Advocacy Conference (JAC) 2015, Washington, DC. Sponsor: AUA and AACU (American Association of Clinical Urologists)

12-14: Advanced Prostate Cancer Consensus Conference: APCCC, St. Gallen, Switzerland. Sponsor: Janssen

14: 8th Annual Interdisciplinary Prostate Cancer Congress, New York, NY. Sponsor: Physicians’ Education Resource, LLC

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In This Issue

page 1 Featured Opinion; New Agents; Funded Investigators **page 2** Funded Investigators continued **page 3** Spotlight; Calendar of Events; Contact Info

page 4 New Agents continued; Did You Know **page 5** Funded Investigators continued; Program News

page 6 Featured Opinion continued; Grant Writing Tips



Dr. Tomasz Beer

agents provided a variety of ways of exploiting prostate cancer's "Achilles' heel," its hunger for testosterone. But none of these agents managed to improve survival – until 2011.

Indeed, when a comprehensive analysis of older multi-drug hormonal therapy regimens showed that they were probably not better (or were marginally better) than basic surgical or medical castration, most investigators changed course and pursued different avenues of research. The focus of clinical research work turned toward chemotherapy, agents that seek to protect bones from cancer-related destruction, and even immunotherapy. But clues that the hormonal system remains important were plain to see. Patients whose cancer progressed on hormonal therapy nearly always saw their Prostate-Specific Antigen (PSA) rise – and the PSA protein is made in direct response to androgen action. A significant minority of patients saw their cancers respond to second-line hormonal treatments, even though these second-line treatments were not very potent hormonal manipulations. All of these clinical clues, complemented by basic laboratory discoveries, pointed in a clear direction. Our work on the hormonal system was not done yet. For many patients, male hormones remained the principal driver of prostate cancer growth, even on castration therapy.

The challenge was not to find a therapeutic target. That – the hormonal signaling system – was well known already. The challenge was to find more effective ways to block the hormonal system.

Hormone signaling, at its most basic level, relies on two elements: the hormone and the receptor to which it binds. As it turns out, targeting each of these key elements of the system is useful. Abiraterone markedly reduces hormone production. The sup-

pression is much more complete than was possible with older drugs or with surgical castration. Enzalutamide, on the other hand, blocks the androgen receptor, preventing the binding of hormones to it. It does this much more completely than older receptor blockers. These two drugs moved through phase I and II studies rapidly, as their promise became evident early in their testing in patients. The PCRPC-funded Prostate Cancer Clinical Trials Consortium (PCCTC) played a critical role in accelerating the testing of these compounds. Many, but not all, of the early abiraterone studies were conducted by PCCTC investigators. With enzalutamide, the PCCTC contribution was even more remarkable. The entire phase I and phase II program was conducted within the PCCTC. PCCTC investigators assumed leadership roles in the phase III studies that emerged. As a result of PCCTC work, enzalutamide moved through its testing with extraordinary speed. The very first patient to receive enzalutamide signed on to the phase I study in July 2007. The first patient to start treatment in the first of the two phase III studies enrolled in September 2009. The last patient to enroll in the second of the two phase III studies joined in September 2012. Over these five years, 3,056 men with advanced prostate cancer volunteered to take part in studies of enzalutamide.

By June 2014, all the results were in, and abiraterone and enzalutamide both showed substantial, positive impact for patients with metastatic castration-resistant prostate cancer. Both agents displayed significant levels of activity regardless of chemotherapy exposure and both impacted on a broad range of measures, such as survival, progression-free survival, tumor response, quality of life, and others. Never in the history of prostate cancer had we seen a "4 for 4" performance for a series of practice-changing phase III clinical trials that were closely linked by the biology they were targeting.

Where do we go from here? Of course, today's patients with advanced prostate

cancer have important new treatment options. But this may turn out to be just the beginning. The new agents should be studied at earlier stages of prostate cancer to examine their full potential impact. Beyond that, much work is underway to evaluate the possibility of even more impactful results through combinations of the new agents with one another and with other drugs. Further, understanding mechanisms through which prostate cancer eventually escapes and becomes resistant is critical. As we had before, we again see PSA levels rising in the setting of resistant cancers. This is a clue we will not ignore. The hormonal system is still active and still important even after we have tackled it with our latest weapons. Finding even newer and better ways of shutting down that essential hormonal signal that fuels prostate cancer growth is the next challenge we face. We are a significant step closer to solving the prostate cancer problem for men with advanced disease. But we are not there yet. There is more work to be done.

Dr. Beer is a world renowned medical oncologist specializing in prostate cancer research and patient care. He is also a member of the DoD-funded PCCTC and the Stand Up 2 Cancer West Coast Dream Team.

Did You Know...

- ☞ Over its 16-year history of congressional funding, the PCRPC has changed the landscape of prostate cancer biomedical research. PCRPC has supported over 2,600 basic, translational, and clinical research projects aimed at advancing detection, diagnosis, and treatment for prostate cancer patients.
- ☞ According to a recent long-term European study published in *The Lancet* involving over 162,000 men, PSA screening could reduce deaths from prostate cancer by about one-fifth.
- ☞ The most recent report (2010) on prostate cancer in the United States from the Centers for Disease Control and Prevention found that 196,038 men were diagnosed, and 28,560 men died from prostate cancer in that year alone.
- ☞ African American men have significantly higher rates of incidence and death from prostate cancer. The PCRPC supports research to understand this and other health disparities of this disease.

International Metastatic Castration-Resistant Prostate Cancer Phase III Clinical Trials

Trial Name	Drug	Chemotherapy	Number of Patients	Conclusion
COU-AA-301 ¹	Abiraterone	Post	1195	Prolongs survival
AFFIRM ²	Enzalutamide	Post	1199	Prolongs survival
COU-AA-302 ³	Abiraterone	Pre	1088	Prolongs survival and delays chemotherapy
PREVAIL ⁴	Enzalutamide	Pre	1717	Prolongs survival and delays chemotherapy

¹de Bono JS, et al. 2011. *N Engl J Med* 364(21):1995-2005.
²Scher HI, et al. 2012. *N Engl J Med* 367(13):1187-1197.

³Ryan CJ, et al. 2013. *N Engl J Med* 368(2):138-148.
⁴Beer TM, et al. 2014. *N Engl J Med* 371(5):424-433.

In This Issue

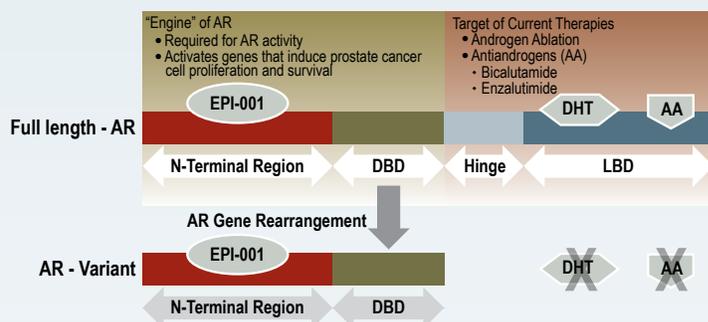


Figure 1. The full length (FL) androgen receptor (AR) is a modular protein consisting of an NH₂-terminal domain, a central DNA binding domain (DBD), a hinge region, and ligand binding domain (LBD) that interacts with dihydrotestosterone (DHT) and antiandrogens (AA) (Note: LBD sites can overlap). Therapeutic resistance can occur through DNA rearrangements in the AR gene leading to fully activated AR variant proteins (AR-V) lacking the LBD, loss of DHT regulation, and loss of inhibition by current therapies. EPI-001 targets the N-terminal region of the androgen receptor instead of the LBD and inhibits the activity of both FL-AR and AR-V.

AR variants in a subset of these patients (39% or 19%, respectively), and found that their presence is likely linked to a patient's development of resistance. Collectively, these findings provide a new understanding of how AR variants can promote treatment resistance in prostate tumors and furnish new clues to therapeutic intervention.

Variations in the AR have also been found in the LBD of the receptor. Taking into account that these LBD mutations are also major contributors to drug resistance, **Dr. Marianne Sadar** of the British Columbia Cancer Agency, with FY04 PCRP funding, used high-throughput screening techniques to search a collection of over 17,000 marine sponge extracts for compounds that are active against both androgen-dependent and androgen-independent prostate cancer cells. She identified EPI-001, a small molecule AR inhibitor that binds to the N-terminal domain instead of the LBD (Figure 1), and determined in preclinical studies that EPI-001 dramatically inhibits the growth of both androgen-dependent and CRPC tumors. With additional PCRP funding support in collaboration with **Dr. Stephen Plymate** of the University of Washington, she showed that EPI-001 inhibits the growth of prostate cancer tumors that express AR splice variants under conditions where bicalutamide and enzalutamide were ineffective. Thus, EPI-001 is the only known inhibitor of the AR splice variants that are correlated to CRPC, poor prognosis, and therapeutic resistance.



Dr. Vivek Arora

Dr. **Vivek Arora** of Memorial-Sloan Kettering Cancer Center also received PCRP funding to investigate mechanisms of resistance to enzalutamide, and he

found that blocking the AR induced the expression of another steroid hormone receptor, the glucocorticoid receptor (GR). Dr. Arora demonstrated that tumor growth was dramatically reduced when the GR was blocked in some prostate tumors resistant to enzalutamide, suggesting that combined inhibition of both the GR and the AR could prolong the duration of response to next-generation AR inhibitors.

Another avenue for CRPC drug development is based on recent compelling evidence that oxidative stress is a major contributor to prostate cancer occurrence and progression. PCRP-funded investigator **Dr. George Wilding** of the University of Wisconsin explored whether antioxidants might be useful as chemopreventive agents for prostate cancer. He found that a segment of the natural antioxidant vitamin E interacts directly with the AR, leading to the development of a potent AR inhibitor, APC-100, which also has antioxidant activity. Preclinical studies proved that APC-100 delays tumor progression and increases survival, and APC-100 is currently in phase II clinical trials within the PCCTC as a treatment for men with CRPC.

From "A"PC-100 to "Z"ytiga, PCRP investigators have played a significant role in establishing the next generation of AR therapies as frontline regimens for the treatment of CRPC. Despite the resistance that may occur, drugs such as abiraterone and enzalutamide can significantly extend the lives of men with CRPC, and PCRP investigators remain dedicated to the study of this family of drugs. A deeper understanding of the roles of androgen synthesis, AR function, and mechanisms of treatment resistance promises to aid investigators in reaching their goal of developing the next generation of new, improved therapies that will further extend life, enhance quality of life, and even cure patients with CRPC.

Program News

- The PCRP received \$80 million in congressional appropriations in January for fiscal year 2014 (FY14). The PCRP Integration Panel outlined 12 award mechanisms for FY14, and program announcements for these mechanisms were released in May 2014.
- Dr. Philip Arlen, M.D., President, Chief Medical Officer, and Chief Executive Officer of Precision Biologics, Inc., assumed chairmanship of the PCRP Integration Panel at the FY14 Vision Setting Meeting in March 2014. Dr. Arlen will hand over the chairmanship of the Integration Panel to Dr. Timothy McDonnell, M.D., Ph.D., Professor and Deputy Chair of the Department of Hematopathology at the University of Texas MD Anderson Cancer Center, in February 2015 to lead the panel through FY15.
- Expert prostate cancer scientists and clinicians and consumers will be meeting in late 2014 and early 2015 to review new applications for FY14 PCRP award mechanisms. Over 900 applications will be reviewed, and final funding recommendations are expected to be announced in February 2015.
- The PCRP-funded Prostate Cancer Biorepository Network (PCBN) was expanded in 2014 through the addition of 1-2 new resource sites: University of Washington and Memorial Sloan-Kettering Cancer Center will join Johns Hopkins University and New York University. In order to expand the PCBN's capability to provide biospecimens that are unique and/or in limited supply, the PCRP is also planning to add 1-2 more resource sites to the PCBN in 2015, focusing on the need for rare samples for future prostate cancer research projects.
- Supported by the PCRP since 2005, the Prostate Cancer Clinical Trials Consortium (PCCTC) has become an official incorporated entity, called the Prostate Cancer Clinical Trials Consortium, LLC. The consortium has executed over 20 service agreements with outside sponsors, including Medivation and Genentech, and has been recognized as a qualified vendor by Novartis. The establishment of the PCCTC, LLC will allow for continued sustenance of the consortium and its contributions to advancing clinical research for prostate cancer.

In This Issue

now know that overexpression of the AR and promiscuous mutations within the AR lead to resistance to antiandrogens (including enzalutamide and abiraterone) in CRPC. Adding more complexity to the promiscuous nature of AR, is sizzling evidence implicating truncated AR splice variants (AR-Vs), which lack the ligand binding domain (LBD), as principal drivers of resistance to antiandrogen therapies. The occurrence of AR amplifications, mutations, and splice variants in castration resistant patients points to such genomic adaptations as key contributors to therapeutic failure by permitting AR signaling despite androgen deprivation therapy. Probing patient blood samples for lethal metastatic cancer cells that can be traced directly back to the primary tumor of origin and that harbor genomic changes (such as AR mutations, PTEN deletion, or TMPRSS2:ERG fusions) can provide us with the ability to detect metastatic spread during the course of therapeutic treatment and redirect therapeutic efforts towards elimination of resistance and lethal disease. Valuable new mechanistic insights into these “drug-gable” oncogenic events can be learned from pre-clinical studies using engineered mouse models harboring distinct signatures consisting of recurrent genomic aberrations (chromosomal losses, gains, rearrangements, and gene mutations) in order to determine the impact of the tumor microenvironment in prostate cancer metastatic progression.

One may argue that the challenge in overcoming resistance to endocrine therapy is the tremendous tissue heterogeneity in the landscape of prostate tumors. Indeed progression of CRPC is dependent on factors produced by the tumor microenvironment that help to increase the essential supply of blood to the tumor (i.e. angiogenesis), and increase invasion and survival of tumor cells. Since both the tumor and the microenvironment are under selection pressure by treatment regimes, they both undergo adaptations resulting in therapeutic resistance. Identifying additional genomic alterations that drive the metastatic spread of cancer cells becomes crucial to combating therapeutic resistance. To the call for cloning of circulating genetic material to help plan chemotherapy and antiandrogen treatment in CRPC patients, two recent studies by Luo (supported by the PCRP) and Attard responded beautifully by introducing sequential monitoring in patients with advanced prostate cancer, and defining a critical role for AR variants in the therapeutic resistance to antiandro-

gens. The emerging promise is that analysis of circulating tumor genomic material from patient blood samples can help to optimize and personalize therapeutic strategies.

The recent PREVAIL study involving men with metastatic CRPC treated with enzalutamide before chemotherapy, revealed an increase in patient survival to 17 months. Having recognized that this is a significant increase in survival, do we find ourselves asking with hope whether we can actually do better, extend that survival to more than 5 years, perhaps even 10 years in this subpopulation of patients? The stage-specific response to therapeutic strategies (with taxane chemotherapy being more effective at later stages of prostate cancer progression than antiandrogens) has taught us that prostate cancer undergoes an evolution during disease progression. Ongoing efforts coordinated by the PCRP Clinical Consortium and fueled by the Transformative Impact Award supporting Steve Plymate’s work on targeting the aberrant AR in advanced treatment-resistant prostate cancer, aim to understand the genomic causes of treatment failure and resistance to androgen signaling targeting, as well as to taxane chemotherapy and build a new molecular scenario, whereby individual drugs would be replaced by a sequencing strategy of multiple drugs targeting cancer cells with specific mutations.

Careful interpretation of these exciting clinical findings will enable us to disrupt the lethal disease progression in patients with CRPC. The PCRP can meet this new challenge through the vision of its leadership and focus on the cause. The PCRP has not only maintained a strong momentum in the discovery process, but it consistently plays a crucial role in the implementation of cutting-edge, paradigm-shifting science that is having a major impact on patients, through enabling the transition of scientific breakthroughs from the laboratory to the clinic, and empowering the training of a new generation of physician-scientists to carry the torch. The results of this commitment to innovative and translational research have led to interrogation of the molecular landscape of prostate cancer, and to the development of personalized medicine approaches applied with finesse and mechanism-driven understanding. The return on this intellectual investment has been phenomenal as valuable answers keep coming towards eliminating pain, suffering, and ultimately death due to metastatic prostate cancer, while new opportunities are presented at a vigorous pace to improve

the quality of life in all men affected by prostate cancer.

Dr. Kyprianou is a leading investigator in prostate cancer research and is an internationally recognized expert in Urology, Molecular and Cellular Biochemistry, Pathology and Toxicology. She has served on the PCRP Integration Panel since 2008.



PCRPs Grant Writing Tips

- Each award mechanism places importance on different criteria, which are listed in the “Application Review Information” section of each Program Announcement. Be sure that your application specifically addresses each of the review criteria.
- Be sure to submit your application well ahead of the submission deadline! You can still make changes to your application after it has been submitted, and there will be no last-minute surprises or issues uploading documentation.
- In accordance with the ARRIVE guidelines published in Nature in 2012, the CDMRP is emphasizing that if animal models are being used, consult the ARRIVE guidelines to ensure relevant aspects of animal research are adequately planned for and well described in your application.

**Watch for more tips
in the next issue!**

**Visit the PCRPs Webpage for
Up-to-Date Program Information**
<http://cdmrp.army.mil/pcrp/default.shtml>

The DoD PCRPs 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.

In This Issue