CDMRP
Department of Defense
Prostate Cancer Research Program (PCRP)

PCRP erspectives

Volume 5, Number 1 – September 2015

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Featured Opinion

Rebuilding Our Defenses: Exploiting Immune Mechanisms to Fight Prostate Cancer

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

One of the most exciting areas in all of oncology is the study of immunotherapy, the ability to harness the body's own immune system to attack cancer cells. The immune system is composed of white blood cells and organs and tissues of the lymph system, and helps the body fight infection and disease. Different types of immunotherapy consist of monoclonal antibodies, adoptive cell transfer, cytokines, and cancer vaccines. Monoclonal antibodies, which are drugs designed to bind to specific targets in the body, can cause an immune response that destroys cancer cells. Adoptive cell transfer is a treatment that helps boost the natural ability of T cells to fight cancer. T cells are a type of white blood cell and are part of the immune system. Cytokines are proteins made by the body's cells and play important roles in normal immune responses and the immune system's ability to respond to cancer. Cancer vaccines work against cancer by boosting the immune system's response to cancer

» continued, **SEE OPINION, PG. 6**

The Evolving Role of Immunotherapy in Prostate Cancer

Celestia S. Higano, M.D., FACP, University of Washington

The role of immunotherapy in treating cancer is changing rapidly. At one time, only melanoma and renal cancers were thought to be amenable to immunotherapy. However, at the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting, effective immunotherapy approaches were reported in a variety of cancers including cervical, pancreatic, bladder, lung, brain, colon, and numerous others, in addition to prostate cancer (PCa).

Sipuleucel-T (Provenge®) is a cellular vaccine made from the patient's own immune cells that are stimulated to respond to prostatic acid phosphatase, an antigen present on most PCa cells. To date, it is the only FDA-approved therapeutic cancer vaccine. Approval of sipuleucel-T was based on demonstration of improved overall survival in the Phase III IMPACT (Immunotherapy for Prostate Adenocarcinoma Treatment) study in men with metastatic castration-resistant prostate cancer (mCRPC) who had no, or minimal, symptoms.[1] In recent years, two additional PCa vaccines have moved into Phase III clinical trials based on encouraging findings in Phase II trials.[2-3] PROSTVAC® is a recombinant cancer vaccine administered by subcutaneous injection designed to enhance the immune response to prostate-specific antigen (PSA). This trial has completed

» continued, **SEE IMMUNOTHERAPY, PG. 4**

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

Today's patient with advanced PCa has access to a variety of new treatment options, many of which have provided significant improvement on a broad range of patient response measures such as survival, tumor response, and quality of life. While hormone-based therapies such as abiraterone (ZYTIGA) and enzalutamide (XTANDI) are often the most logical approach to combatting PCa's Achilles heel – the androgen receptor – other treatment options are available that attack the tumor from a different angle – by training the body's own immune system to fight tumors. Cancer immunotherapy made headlines with the approval of sipuleucel-T (Provenge) for PCa. It is a personalized treatment that works by reprogramming a patient's own immune system to seek out and destroy cancer cells, regardless of their location in the body. However, this immunotherapy is expensive and, like other treatments for advanced PCa, is not curative.

While this technology was being developed, PCa immunologists were seeking

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

VISION: Conquer prostate cancer.

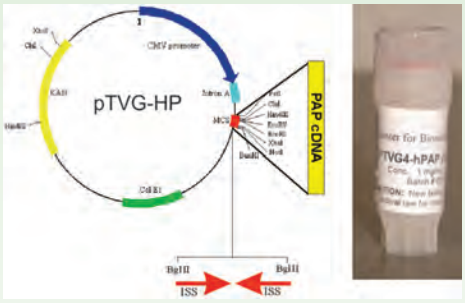
MISSION: Fund research that will lead to the elimination of death from prostate cancer and enhance the well-being of men experiencing the impact of the disease.

» FUNDED INVESTIGATORS CONTINUED FROM PG. 1

to unravel the complexity of the immune system and harness its power to conquer PCa. Cancer cells express tumor-specific antigens, which are proteins different from those typically present in healthy tissue. Several innovative technologies are being developed to deliver tumor-specific antigens to patients: peptide-based, DNA-based, and cell-based (e.g., dendritic or T cells) vaccines, which stimulate the body's immune system to seek and destroy cells carrying these antigens, i.e., tumor cells. PCRP investigators have made major contributions to understanding the immune response to PCa in an effort to develop more effective immunotherapies and to develop marker-based diagnostic tests for PCa.

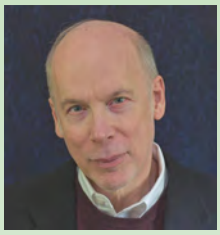
During the PCRP's early years, immunology research was focused on better defining prostate tumor antigens and developing simple immunotherapeutic approaches for treating PCa. In 1999, PCRP-funded investigator **Dr. Douglas McNeel**, a postdoctoral fellow at the University of Washington, discovered that patients with PCa have pre-existing immunity to prostatic acid phosphatase (PAP), a protein commonly overexpressed in metastatic PCa, and that immune cells, specific for PAP, can destroy PCa cells. Transferring to the University of Wisconsin as an assistant professor, Dr. McNeel further developed a DNA vaccine encoding PAP (pTVG-HP); he showed that the vaccine elicited an immune response to PCa tumors in animal models, suggesting this approach might work in humans. Dr. McNeel initiated clinical trials of the PAP DNA vaccine in PCa patients, and PCRP-funded Phase I trial results demonstrated that the DNA vaccine, administered by a simple intradermal injection (similar to a flu shot, and not requiring leukapheresis), elicits a measurable immune response. After receiving this vaccine, some patients with rising PSA after prostatectomy or radiation therapy experienced prolonged PSA doubling times that persisted over a year. An ongoing Phase II trial to test whether this vaccine delays the development of metastases is being conducted under the PCRP's **Prostate Cancer Clinical Trials Consortium** (final results expected in 2017).

Dr. Douglas McNeel

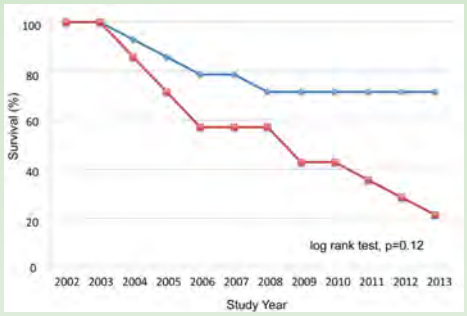


Schematic diagram of the DNA vaccine encoding PAP (pTVG-HP) and photograph of a clinical-grade vaccine vial.

PCRP investigators have also explored other prostate tumor antigens as simple immunotherapies including PSA, usually associated with PCa diagnosis and also used extensively to follow PCa therapy. **Dr. David Peace** of the University of Illinois (Chicago) identified amino acids 146-154 as the most immunogenic region of PSA; then, in the first clinical trial of a peptide vaccine in PCa, he demonstrated that intradermal injection of PSA 146-154 peptide induces a strong, lasting immune response capable of destroying prostate tumor cells in 50% of patients with advanced disease. In a follow-up study 6 years after the patients were first vaccinated, Dr. Peace observed a trend toward increased survival in patients who initially displayed a strong immune response compared to those who did not. Today, Dr. Peace continues working to improve the PSA peptide vaccine, and he states, "After 10 years, I still find the survival data intriguing."



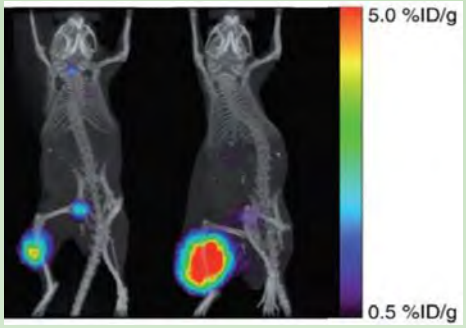
Dr. David Peace



Ten-year overall survival of PCa patients (n=14) vaccinated with PSA 146-154 peptide who mounted an immune (delayed type hypersensitivity) response within one year of immunization (blue) compared to those (n=14) who did not develop an immune response (red).

Prostate stem cell antigen (PSCA), another tumor cell antigen, was discovered by UCLA's **Dr. Robert Reiter** in 1997. PSCA is a cell surface protein expressed in the stem cell compartment of the normal prostate and is overexpressed in a majority of localized and metastatic prostate cancers. Dr. Reiter had previously developed a monoclonal antibody against PSCA, called mAb 1G8, and with PCRP funding, he demonstrated that this antibody is capable of killing PCa cells and inhibiting tumor growth and metastasis of PCa in mouse models. More recently, with funding from a Laboratory–Clinical Transition Award, he developed and tested a radio-labeled (I-124) PSCA antibody (called a minibody) for positron emission tomography imaging and demonstrated that it possesses excellent immunoreactivity and imaging contrast in animal models of PCa. A clinical trial for imaging PCa metastases in patients using this minibody is underway. Similarly, **Dr. Michael Kinch** of Purdue University developed an antibody to a receptor tyrosine kinase (EphA2), which is overexpressed in many PCa cases and correlates to tumor cell aggressiveness. He demonstrated that this EphA2 antibody selectively recognizes PCa cells and inhibits prostate tumor growth in animal models. The EA5 antibody was subsequently licensed to MedImmune, now working to develop an antibody drug conjugate (MEDI-547) to selectively target and deliver lethal drugs to PCa cells.

Dr. Robert Reiter



I-124-anti-PSCA immuno positron emission tomography imaging of mice bearing PCa intra-tibial xenograft tumors. Increased uptake of anti-PSCA minibody can be easily discerned in the tumor-bearing tibias (Knowles et al. Clin Cancer Res. 2014; 20:6367-78).

PCRP researchers are developing new technologies by bundling prostate tumor antigens together to generate more robust vaccination approaches. Dendritic cell (DC)-based vaccination, although a promising strategy for PCa immunotherapy, has achieved limited success in PCa, in part because of suboptimal activation of immune

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Spotlight

Willie Staten: "You can make excuses or make your life a testimony"

It is very important for people to find opportunities to serve their communities. I've always been a passionate advocate for a number of different causes, such as helping veterans navigate and process paper work to receive their benefits, and transporting members of my church and community to their doctor's appointments. I also help elderly neighbors with the upkeep and landscaping of their property when they can no longer do so. This activity allows me to further pursue my interest in gardening, which I consider a form of therapy. All of these efforts I felt would benefit the common good of our community, whether it be at a macro, mezzo, or even micro level. I always say a person can either have a complaint or a testimony. This means when things are difficult, you can decide to sit down and complain, or you can decide to use your resources and talent to solve the problem, thereby providing a testimony of your efforts to others.

It was 2005; I'd just finished exercising when I got a call from my urologist. He told me I had prostate cancer; his words left me in complete shock; the experience was very surreal. The doctor asked my wife and me to come in to discuss options. He presented us with a lot of information and it was a little overwhelming. He described several options for treatment – I would need to decide whether I should go with radical prostatectomy, radiation pellets, or active surveillance, and so on. Once the urologist confirmed I had an aggressive form of prostate cancer, I elected to have a radical prostatectomy.

In the immediate aftermath of my diagnosis and treatment, I had to focus my efforts on getting better and helping other family members who were also dealing with serious health issues. Once I felt better, I joined Us TOO International. The act of talking to other men who were dealing with similar concerns was a great form of therapy. The support group provided various opportunities to learn and share information with other survivors and patient advocates. Because of my experiences with Us TOO, I was motivated to once again contribute to my community by talking to men about prostate cancer. I was even able to help my brother. When talking with him one day, I discovered he had not seen a doctor in some time, nor had his PSA been checked. I encouraged him to make an appointment and, as a result, he learned he had advanced prostate cancer. From this experience, I again realized the impact that each person can have in another person's life.

I was grateful for the nomination by Us TOO International to participate as a consumer reviewer in the PCRP peer review process. I think my previous career history as a Combat Medic, Radiography Technician, Respiratory Therapist, Social Worker, and Instructor served me well on the review panels. PCRP-funded projects have resulted in new findings for the prevention and treatment of prostate cancer, and I was encouraged to learn that scientists are continuing to develop better tests to improve diagnosis and prognosis for prostate cancer patients. It's good to know potential treatments are on the way and that fewer men will suffer. Based on my experiences serving on a PCRP panel, I think there is great promise to seeing the eradication of prostate cancer.

I'm glad I had this volunteer experience. Everyone can do something; find out what motivates you. I can't think of a better way to give back to your community, to work with other survivors, advocates, and scientists to improve the lives of those living with prostate cancer. This will be part of my testimony. We can complain because rose bushes have thorns, or rejoice because thorn bushes have roses.

Did You Know...

- According to the American Cancer Society, over the past two decades, death from prostate cancer has declined nearly by half, and prostate cancer rates have decreased by 2.1 percent per year.
- According to the American Cancer Society, African Americans, in comparison with white males, are usually diagnosed about 3 years younger on average and are more likely to have "high grade" tumors that rapidly grow and spread.
- Ralph Steinman, M.D., of Rockefeller University won the Nobel Prize in Physiology or Medicine in 2011 for work he published as a postdoctoral fellow in 1973 for his discovery of the central role of dendritic cells in adaptive immunity.
- The PCRP is the second largest funding organization for prostate cancer research, following the National Institutes of Health.
- On average, more than 60 prostate cancer survivors from over 20 organizations participate in PCRP peer review each year.

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

http://cdmrp.army.mil/pcrp

The DoD 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.

To subscribe to this free newsletter, please contact the editor at usarmy.detrick.medcom-cdmrp.mbx.cdmrp-public-affairs@mail.mil

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accrual, and results are expected in the next few years. DCVAC®, also a cellular immunotherapy like sipuleucel-T, uses the patient's immune cells exposed to an array of antigens derived from killed PCa cells instead of a single PCa antigen. Patients on this trial receive docetaxel alone or in combination with DCVAC®.

After FDA approval of sipuleucel-T for mCRPC in 2010, clinicians and scientists, many of whom are members of the PCRP-funded Prostate Cancer Clinical Trials Consortium (PCCTC), focused on ways to optimize the benefits of sipuleucel-T. One approach is to use sipuleucel-T, alone or in combination with androgen deprivation therapy (ADT), earlier in the course of the disease rather than after metastases have developed. **Dr. Larry Fong** of the University of California, San Francisco, was the first to show that, when given before prostatectomy, sipuleucel-T causes an increase in activated T cells in the prostate compared to no therapy, thus demonstrating that sipuleucel-T results in an immune response in the tumor. **Dr. Tom Beer** of Oregon Health & Science University treated men who had a rising PSA after radical prostatectomy with ADT followed by either sipuleucel-T or observation. Men who received sipuleucel-T had a lengthening of the PSA doubling time relative to the observation group, suggesting that sipuleucel-T slows tumor growth. **Dr. Emmanuel Antonarakis** of Johns Hopkins University and members of the PCCTC have also looked at the timing of sipuleucel-T with ADT in men with rising PSA levels after primary treatment, asking whether it is better to give the vaccine before, during, or after ADT. Preliminary data suggests that the immune responses are superior when ADT is given before administration of sipuleucel-T.

In metastatic disease, sipuleucel-T is being combined with other agents also known to improve overall survival. In one PCCTC trial, Dr. Antonarakis is combining sipuleucel-T with radium-223 (Xofigo®), an alpha-emitting radioisotope localizing in bone, which was FDA-approved for the treatment of men with mCRPC and bone metastases.

Efforts to find "biomarkers" that will predict who will respond to immunotherapy are also in progress. In the original IMPACT trial, it was observed retrospectively that African American men treated with sipuleucel-T displayed a greater improvement in overall survival as compared with European American men. *(McLeod DG, et al. 2012. AUA Annual Meeting, Atlanta, Georgia. Abstract 953).* **Dr. Larry Lum** at Wayne State University will prospectively compare the immune responses of African American and European American men treated with sipuleucel-T in an effort to identify biomarkers of response.

Another approach to immunotherapy is to interfere with signals or "checkpoints" that inhibit the body's ability to mount an effective immune response. Blockade of checkpoints can be accomplished with either anti-CTLA4 antibody or PD1 inhibitors that have been shown to induce tumor regression and improve survival in other cancers without vaccination. Ipilimumab, a monoclonal antibody to CTLA4, has been studied in PCa as well as in renal cell cancer and melanoma, and was FDA-approved for metastatic melanoma in 2011. In a Phase I/II trial conducted by the PCCTC, **Dr. Susan Slovin** of Memorial Sloan Kettering Cancer Center studied the effect of a single dose of radiation to bone to kill cancer cells (and release tumor antigens) followed by ipilimumab to turn off inhibition of T cell immune responses in men with mCRPC. Results of this study, including PSA declines and tumor shrinkage, provided evidence for the design of a Phase III trial started in 2009. Men with mCRPC who had progressed after docetaxel, were treated with radiation followed by ipilimumab or placebo. In September 2013, it was reported that this trial did not meet its primary endpoint of improving overall survival. However, a subset of patients with bone metastases but no spread to liver and/or lungs treated with ipilimumab showed a survival benefit which led to a second Phase III study.[4] In this study, initated in 2010, men with mCRPC who had never received docetaxel and did not have liver or lung metastases were randomized to ipilimumab or placebo. Results from this trial are expected in the near future.

Combinations of immunotherapy drugs also look very encouraging. At the 2015 ASCO Annual Meeting, a Phase I trial of PROSTVAC® and ipilimumab demonstrated that the overall survival of men treated with the combination lived significantly longer than expected. In late 2015, the combination of a vaccine, a checkpoint inhibitor, and an oral immune modulating agent studied in animal models is scheduled for study in humans for the first time.

In addition to vaccine and checkpoint inhibitors, other novel immunotherapy approaches are in development. **Drs. Celestia Higano and Larry Fong** are conducting a PCCTC "first in man," dose-finding Phase I trial of ES-414, a biphenotypic antibody that couples T cells to PSMA on the surface of PCa cells, enhancing T cell activation and proliferation, and causing tumor cell destruction.

Despite the fact that there is currently only one immunotherapy available to treat men with PCa, it is likely that more agents or combinations of agents will become available over the next 2 to 5 years. During that time, as we gain greater understanding of the immune system and define biomarkers, we are likely to acquire new treatments and to better choose patients who are more likely to benefit from immunotherapy. There is no doubt that the next decade will produce exciting immunotherapy treatment options for cancer patients, including men with PCa.

Dr. Celestia Higano

Dr. Higano is a medical oncologist at Seattle Cancer Care Alliance who specializes in treating PCa. She is a Professor of Medicine and Urology at the University of Washington School of Medicine, and a member of the Clinical Research Division, Fred Hutchinson Cancer Research Center.

References:

1. *Kantoff PW, et al. IMPACT Study Investigators. 2010. Sipuleucel-T immunotherapy for castration-resistant prostate cancer.* N Engl J Med *363(5):411-422.*
2. *Kantoff PW, et al. 2010. Overall survival analysis of a Phase II randomized controlled trial of a Poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer.* J Clin Oncol *28(7):1099-1105.*
3. *Podrazil M, et al. 2015. Phase I/II clinical trial of dendritic-cell based immunotherapy (DCVAC/PCa) combined with chemotherapy in patients with metastatic, castration-resistant prostate cancer.* Oncotarget *6(20):18192-18205.*
4. *Kwon ED, et al. 2014. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): A multicentre, randomised, double-blind, Phase III trial.* Lancet Oncol *15(7):700-712.*

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Dr. Pawel Kalinski

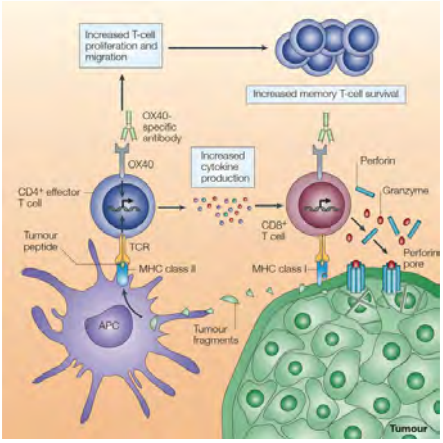
cells. To overcome this problem, **Dr. Pawel Kalinski** of the University of Pittsburgh (with funding from a Clinical Trial Development Award) developed a clinical protocol that takes DCs from the patient's own blood and cultures them with growth factors/cytokines that imitate the inflammatory conditions of viral infections, enhancing their ability to induce an immune response. The cells are then incubated with antigens derived from a dead PCa cell line and re-infused into the patient. This enhanced DC vaccine (alpha-type-1-polarized DCs) is being tested in a University of Pittsburgh Cancer Institute-funded Phase I clinical trial. Thus far, the treatment has been well tolerated in all 10 treated patients. The final findings are expected to be published in 2016.

Although the DC-based vaccine sipuleucel T is validated for clinical use, its manufacture is expensive and the scope of the immune response is limited. To overcome these limitations, **Dr. Dirk Brockstedt** of Aduro Biotech in collaboration with Dr. McNeel of the University of Wisconsin, and with funding from a Laboratory–Clinical Transition Award, is developing a live-attenuated Listeria monocytogenes vaccine that directly targets a patient's DCs. This approach is an improvement over existing methods that require a patient to undergo leukapheresis. Moreover, instead of using only one antigen, as sipuleucel T does, this vaccine uses a unique combination of four well-defined PCa antigens commonly overexpressed in prostate tumors and PCa stem cells. The idea is that the DCs will take up the vaccine, and the resulting immune response to all four tumor antigens will be more effective than the response to vaccines that target only one antigen. This novel vaccine technology was licensed to Janssen Biotech, Inc. and is moving rapidly toward clinical trials.

Just as many patients develop resistance to chemotherapy and hormonal therapy, the body can develop resistance to immunotherapy. Identifying the mechanisms by which prostate tumors evade the immune response to tumor antigens and finding ways to enhance antitumor immune response has proven to be a promising approach in PCa treatment. **Dr. Andrew Weinberg** of the Providence Portland Medical Center demonstrated that an antibody that activates OX40, a protein on the surface of immune cells, increased immune cell proliferation and, in combination with other therapies, enhanced antitumor activity and survival in a preclinical model of PCa, thereby showing the potential value of adding OX40 to immunotherapies. More recently, Dr. Weinberg has developed an OX40L:Ig fusion protein for use in humans that is capable of enhancing T cell stimulation and promoting the immune system's potential to kill tumor cells. This technology was licensed to Medimmune, which has helped to further advance its biologic activity, and is in a clinical trial in advanced cancer patients (now called MEDI6383).


Dr. Andrew Weinberg

PCRP-funded researchers have made outstanding contributions toward understanding the immune response in PCa and are making progress in their efforts to harness its power. New tumor antigens have been discovered, antibodies developed, and vaccination strategies established. Many of the early, basic studies funded by the PCRP have transitioned from bench to bedside, with several resulting technologies being acquired by the pharmaceutical industry. The current challenge is how to integrate these new immunotherapies with the many new agents that have been shown to extend life, and to determine whether immunotherapy has a role much earlier in the course of the disease.



Agonist OX40-specific antibodies can elicit enhanced CD4+ T cell responses (through increased cytokine production and increased survival of memory T cells) and CD8+ T cell responses (through increased perforin and granzyme production), leading to tumor-cell killing.

Calendar of Events

September

S	M	T	W	T	F	S
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6	7	8	9	10	11	12
13	14	15	16	17	18	19
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27	28	29	30			

11–13: 2015 Prostate Cancer Conference. Los Angeles, CA. Sponsor: Prostate Cancer Research Institute.

24: Application deadline for IDA, IA, and ERA

27–30: CRI-CIMT-EATI-AACR–The Inaugural International Cancer Immunotherapy Conference: Translating Science into Survival. New York, NY. Sponsors: the Cancer Research Institute (CRI), the Association for Cancer Immunotherapy (CIMT), the European Academy of Tumor Immunology (EATI), and AACR.

October

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15–16: The New and Continuing EDRN Principal Investigator Orientation. Bethesda, MD. Sponsor: NIH.

21–23: 2015 International Cancer Education Conference. Cancer Education in Diverse Populations: Disparities, Genomics, and Innovations. Tucson, Arizona. Sponsor: American Association for Cancer Education.

November

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5–9: AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics. Boston, MA. Sponsors: AACR, the National Cancer Institute (NCI), and the European Ogranisation for Research and Treatment of Cancer (EORTC).

Program News

- In February 2015, the PCRP completed the peer and programmatic review processes for FY14. The program received 887 compliant applications in response to the 12 funding opportunities offered in FY14.
- Congress provided $80M in appropriations to the PCRP for FY15, and the Integration Panel convened in February 2015 to develop the priorities and investment strategy. This year, seven different PCa research funding opportunities are available that prioritize innovation, impact, and training for young investigators.
- Dr. Timothy McDonnell, M.D., Ph.D., Professor and Deputy Chair, Department of Hematopathology at the University of Texas MD Anderson Cancer Center, assumed the chairmanship of the PCRP Integration Panel at the FY15 Vision Setting Meeting in February 2015. The Integration Panel also welcomed four new members to the panel; a full list of FY15 panel members is available on the CDMRP website (http://cdmrp.army.mil/pcrp).

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cells. It is believed that the immune system can naturally detect and destroy abnormal cells and may prevent the development of many cancers. However, some cancers are able to avoid the immune system's detection and destruction. They may produce signals that reduce the immune system's ability to detect and kill tumor cells, or they may have changes that make it harder for the immune system to recognize and target them.

In the past, we had a limited understanding of the complexity of the immune system, resulting in the failures of immune-based approaches to treat cancer. However, in recent years our understanding of the complexity has resulted in the development of the first vaccine for cancer, Provenge, which received FDA approval based on its ability to increase overall survival in men with asymptomatic, metastatic PCa prior to chemotherapy. This breakthrough exemplifies the promise that immunotherapy holds in the ability to restore or enhance an individual's immune system to fight cancer. The rapidly advancing field of cancer immunology has produced several new methods of treating cancer that increase the strength of immune responses against tumors. These therapies either stimulate the activities of specific components of the immune system or counteract signals produced by cancer cells that suppress immune responses. Increased research support in the area of immunotherapy, including the PCRP's contributions to both leading and emerging investigators in this field, have expanded our understanding of the immune system. This has helped to accelerate the groundbreaking work that is being translated from the laboratory to immune-based therapies for patients with PCa. The PCRP has funded to a large degree the research that has led to important advances in areas including inflammation, cancer vaccines, antibody conjugates, and immune enhancement via Ipilimumab and OX-40L.

In FY03, the PCRP funded groundbreaking work by Dr. Michael Karin identifying a mechanism for the development of castrate-resistant PCa from an inflammatory response involving lymphotoxin and NF-kB during ADT. Results of this work suggested that therapeutic interventions that prevent lymphotoxin production and/or signaling during ADT could delay the emergence of androgen-independent PCa in humans by up to 2–3 years. In the field of cancer vaccines, the PCRP has encouraged investigators to take early steps in developing treatments that may positively impact the lives of men with PCa by developing DNA- and peptide-based vaccines that target immunogenic epitopes on proteins commonly expressed by PCa cells, and these have shown promising results in clinical trials. More recently, the PCRP has also funded exciting research by Dr. Dirk Brockstedt, with Aduro Biotech, to develop a Listeria vaccine for PCa. Aduro Biotech has recently announced promising Phase IIa results with their Listeria vaccine for pancreatic cancer. Toxicology studies to support an Investigational New Drug application for the PCa vaccine ADU-741 are being initiated based on the previous 8 months of preclinical testing. Other novel efforts funded by the PCRP have examined the limitations of DCs to deliver a tumor-associated target to the immune system and ways to overcome these limitations. Another significant recent advance in immunotherapy has been the evolution of agents to remove the "brakes" on the immune system and to allow for a more sustained immune response. Finally, novel methods to enhance T-cell killing activity have also been funded by the PCRP.

The PCRP continues to play a very important role in funding cutting-edge, disruptive research in the field of PCa. These approaches were derived from novel discoveries in the laboratory examining how the immune system works. Checkpoint inhibitors such as ipilumimab that allow for the immune system to continue its work are a prime example of this. The additional research studying how co-stimulatory molecules activate T-cells to fight cancer has also been translated into the clinic through the novel vaccine Prostvac, as a therapy for PCa. There was a time not too long ago that research in tumor immunology was frowned upon in the scientific community. However, the PCRP continued to fund innovative ideas in this area, which has led to a significant understanding of how the immune system works and how an individual's own cells can be taught to destroy cancer. The PCRP has set several overarching goals toward improving the lives and outcomes of men with PCa. It has and will continue to play a significant role through funding exciting new developments in basic tumor immunology and translating this research into breakthroughs in the treatment of PCa. The journal *Science* designated "immunotherapy of cancer" as its Breakthrough of the Year in 2013 to recognize the progress made in this area. However, with the many new discoveries, there is still a need to explore how to incorporate these advancements in immunotherapy to patients with PCa. Since many of these therapies utilize different immune mechanisms, how can they be used both safely and effectively in the clinic to produce significant beneficial outcomes to patients with PCa? Combination strategies are illuminating the new avenues of research, and the future of immunotherapy has never looked brighter.

Dr. Arlen is a board-certified medical oncologist and internationally renowned expert in tumor immunology, immunotherapy, and cancer vaccines. He has served on the PCRP Integration Panel since 2008.

PCRP Grant Writing Tips

- Some FY15 award mechanisms provide multiple options to applicants, such as applying as an experienced or young investigator, or applying as an individual or part of a research team. Be sure to carefully review the components and requirements for each, and make sure your application addresses all the important points under those options.
- Submit your application well ahead of the submission deadline! You can still make changes after it's been submitted, and there will be no last minute issues.
- If you plan to submit a team-based application under a Partnering PI Option, make sure all partnering PIs submit their parts of the application on time, or the application will not be reviewed.

Watch for more tips in the next issue!

For more information:
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