# WRAMC US TOO, Inc.

**A PROSTRATE CANCER SUPPORT GROUP**
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# NEWSLETTER

**VOLUME 14** **NUMBER 4** **NOVEMBER 2005**


## ♦ DEALING WITH PROSTATE CANCER - A PERSONAL STORY ♦

### by Charles O. Paddock

I was diagnosed with prostate cancer in 1999. I had experienced no symptoms, but my PSA had risen slowly from 4.25 ng/ml to 12.3 ng/ml over a period of eight years. At that point, my primary care physician became concerned enough to refer me to a urologist.

The urologist performed a biopsy that gave me the bad news. It showed a Gleason 3+3 adenocarcinoma from less than 5% of the tissue from the right lobe of my prostate. No cancer was detected within the left lobe. Naturally, I was deeply concerned, but I had reasonable assurance that the disease was contained within the prostatic capsule. A bone scan revealed no evidence of metastatic disease.

The urologist recommended surgery and I was inclined to select it. Still, I followed the common wisdom and sought another opinion from a urologist in a different hospital. I also sought the opinions from friends and acquaintances who had had one therapy or another in dealing with their prostate cancer. Finally, I settled on surgery, the so-called "gold standard" at that time. Advances in radiation technology and technique since then have made the radical prostatectomy less "golden," but at that time, I was somewhat predisposed to select it for my primary therapy. Furthermore, I was encouraged by the fact that nerve-sparing was likely in my circumstances.

My post-operative PSA dropped to 0.2 ng/ml. I anticipated that there would be some degree of incontinence, perhaps for as long as a year according to the sources I read. But I would not be so fortunate. My incontinence has persisted to this day - six years! Similarly, I knew that the return of potency would take some time, but again, I was disappointed. Total impotence has been my lot. Incidentally, I experienced diminished penile length similar to that reported in a previous personal account in this newsletter. **(Continued on page 6.)**

## ♦ *INSIDE THIS ISSUE* ♦

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## ♦ FROM THE EDITOR'S DESK ♦

Persons diagnosed with prostate cancer have a wealth of information to help guide them in coping with the disease. The Internet abounds with relevant websites, some of dubious value, and the popular press often reports on new research developments of interest to men with prostate cancer. Most of this information deals with the physical aspects of the disease, but less is said about the psychological issues associated with prostate cancer. Our next quarterly meeting helps remedy this situation. Read below to learn more about this special opportunity.

Our speaker for the August meeting was Dr. James L. Gulley, Director of the Clinical Immunotherapy Group, National Cancer Institute. His topic was "Vaccines for Prostate Cancer - Science and Technology on the Cutting Edge." The presentation gave special insights into promising developments using vaccines as a weapon in the fight against prostate cancer. A summary of Dr. Gulley's remarks begins on page 7.

## ♦ PROGRAM FOR WEDNESDAY, NOVEMBER 2, 2005 ♦

Our speaker for November 2, 2005, is Steven J. Tulin, Ph.D. Dr. Tulin holds degrees in Psychology from Clark University, Cornell University, and the doctorate from the California School of Professional Psychology, Los Angeles. He also completed a post-doctoral fellowship in Rehabilitation and Neuropsychology at the National Rehabilitation Hospital in Washington, DC. Dr. Tulin has been a clinical psychologist within the Department of Psychology, WRAMC, for fifteen years and he has developed a special relationship with men newly diagnosed with prostate cancer and others seeking assistance in coping with the disease. Join us at 7 PM on Wednesday, November 2, 2005, in Joel Auditorium, WRAMC, to hear an experienced practitioner address the psychological aspects of dealing with prostate cancer. Plan now to attend and bring your spouse or a friend. They are always welcome.

**Study Says Viagra Unlikely to Trigger Heart Attack**. There have been isolated reports of heart attacks occurring with Viagra use, but until now, no controlled analyses have been published. Mittleman, et al., at Harvard Medical School did the first large-scale study of the issue. The researchers analyzed the risk of heart attack within 6 and 24 hours after taking Viagra among 9,317 men enrolled in 80 studies during 1993-2000. A total of 69 heart attacks were recorded, but only 22 occurred within 25 hours of Viagra use. The researchers concluded that the absolute risk of heart attack associated with Viagra and presumably sexual activity is small, even in men with erectile dysfunction. The study, funded by Pfizer, maker of Viagra, was recently published in the American Journal of Cardiology. (Source: Reuters Health Information, August 25, 2005, via AOL News)

**Quality of Life after Brachytherapy.** A study by Feigenberg, et al., assessed quality of life for one year after brachytherpy for men with T1c-2a prostate cancer. The 98 patients self-administered three separate quality of life questionnaires during that period. One year after brachytherapy, 80% of the men reported decreased sexual function, and more than 60% of men reported decreased urinary function compared with the baseline. (Source: *Intern'l J Radiation Biol Phys* 2005; 62: 956-64 via Us TOO *Hot Sheet*, August 2005)

**Hormone Therapy and Cognition.** Results of a pilot study suggest that neoadjuvant hormone therapy for early prostate cancer has a modest short-term adverse impact on cognitive function. Jenkins, et al., University of Sussex, UK, found that luteinizing-hormone releasing hormone agonist therapy (LHRH) may cause subtle changes in cognition in this group of patients. The patients in this study received only three months of LHRH therapy whereas many patients receive longer term treatments. The researchers monitored the short-effect of LHRH agonist therapy on patients' memory, concentration, and spatial skills. The thirty-two patients with localized prostate cancer had cognitive assessments before starting hormone therapy combined with radiotherapy. Eighteen men without prostate cancer were also given these cognitive tests. The results showed that for some men undergoing hormone therapy cognitive performance was worse, particularly in spatial skills. The effects were subtle rather than clinical, but a quarter of the men complained of deteriorated memory one year after treatment. Given the increasing use of LHRH therapy, the researchers called for a larger study of the possible side-effects of the treatment. (Source: *BJU Intern'l* 2005; 96: 48-53 via Medscape, July 20, 2005)

**PSA Screening in Men Without Symptoms.** PSA screening for men without symptoms remains controversial, but a recent study indicates that it can significantly reduce the risk of metastatic prostate cancer. Goel, et al., University of Toronto, studied 236 men with metastatic prostate cancer and 462 men in a control group. PSA screening of the men without symptoms reduced their risk of metastatic

prostate cancer by 35%. The risk reduction was even more pronounced among men between ages 45 and 59; it was 48%. The researchers note that randomized trials are underway that should verify or refute their findings. Until then, the researchers say there is "suggestive evidence" that PSA screening of men without symptoms can reduce the risk of metastatic prostate cancer. (Source: *J Urol* 2005 via Medscape Health Information, July 11, 2005)

**Cost/Benefits of Lowering PSA Cutoff.** Researchers warn that lowering the threshold for an "abnormal" PSA from greater than 4.0 ng/ml to 2.5 ng/ml would dramatically increase the number of unnecessary biopsies with no evidence that prostate cancer mortality would be reduced. Welch, et al., VA Medical Center, White River Junction, VT, roughly estimate that 1.5 million men between the ages 40 to 69 - the most likely to undergo screening - have a PSA higher than 4.0 ng/ml, justifying a biopsy. Lowering the "abnormal" threshold to 2.5 ng/ml would add an additional 1.8 million men to the list of those requiring biopsy, if all men were screened. This group of men would comprise 10.7% of all US men between the ages 50 to 59, and 17% of those between ages 60 to 69. For context, only 0.3% of men in their 50s and only 0.9% of men in their 60s are expected to die from prostate cancer in the next 10 years. The researchers contend that, if anything, consideration should be given to raising the cutoff for the "abnormal" PSA cutoff. This would identify men at the highest risk of clinically significant disease, while at the same time limiting the number of healthy men who might be harmed by unnecessary treatment. (Source: *J Natl Cancer Instit* 2005; 97: 1132-1137)

**Eat Right, Work Out, and Reduce Stress to Slow Prostate Cancer.** Ornish, et al., University of California at San Francisco, studied 93 men newly diagnosed with early prostate cancer. The men had decided not to seek immediate treatment, choosing instead to monitor their conditions. Half the men adopted a vegan diet (fruits, vegetables, whole grains supplemented by soy, vitamins and minerals, but no meat, eggs or dairy products). This group also began moderate aerobic exercise and stress management techniques such as yoga and breathing exercises. The other group took no unusual precautions. Both groups had a PSA test at the outset and another one year later. Men in the diet and exercise regimen had a 4 % drop in PSA levels, but the other group had an average rise of 6 percent in PSA. In addition, blood from the diet and exercise group appeared to inhibit growth of prostate cancer cells in laboratory tests. Furthermore, none of those who made the lifestyle changes needed treatment during the study year compared to the other group, six of whom required treatment. Similar results were noted in two recent breast cancer studies. Cautious observers noted the small sample size (93 men), the many variables that were changed in the course of the study, and other caveats. The fundamental issue remains - it has not been demonstrated that lifestyle changes result in men with prostate cancer living longer. Dr. Ornish also emphasized that lifestyle changes are a supplement, and not a substitute for conventional treatment. (Source: *The Washington Post,* Thursday, August 11, 2005, page A6)

**Pomegranate Juice Anyone?** Mukhar, et al., University of Wisconsin, reported that *in vitro* and *in vivo* studies of pomegranate extract demonstrate that it may prevent prostate cancer or slow its growth. Pomegranates are high in polyphenolic

compounds, making pomegranate juice higher in antioxidant activity than red wine and green tea. The researchers incubated prostate cancer cells with pomegranate extract and then observed a dose-dependent inhibition of cell growth due to apoptosis and necrosis. In prostate cancer cells expressing PSA, treatment with pomegranate extract decreased androgen receptor and PSA expression. When human prostate cancer cells were injected into mice, the mice were fed pomegranate extract which delayed the appearance of tumors. Tumor growth was also inhibited and survival was prolonged. The researchers said it was highly unlikely that taking pomegranate juice would produce any adverse effect, and it is highly possible that it would produce useful effects. They added that their studies of pomegranate extract had shown it inhibits skin cancer, and it has the potential to affect other types of cancer. (Source: *Proc Natl Acad Sci USA* 2005, via Reuters Health Information and Medscape, September 26, 2005)

**Post-Prostatectomy Biopsy May Be Unnecessary.** When biochemical failure occurs after radical prostatectomy, a biopsy of the prostatic fossa (former site of the excised prostate) is often performed in order to distinguish local recurrence in the prostatic fossa from metastatic disease. To evaluate detection techniques, researchers at M. D. Anderson Cancer Center, Houston, reviewed 100 men who had failed radical prostatectomies, but had not received subsequent treatment. Overall, prostatic fossa biopsy documented local recurrence in 29 men. The sensitivity of the digital rectal examination in detecting local recurrence was 72.4%. The transrectal ultrasound examination had a sensitivity of 86.2%. None of the men with PSA levels of less than 0.5 ng/ml at time of biopsy had biopsy-proven local recurrence. The researchers concluded that the prostatic fossa biopsy should be avoided in patients with normal digital rectal or ultrasound results and PSA levels below 0.5 ng/ml. (Source: *Urology* 2005; 66:350-355, via Reuters Health Information, September 28, 2005)

**Depression and Cancer.** About 25% of all persons with cancer experience clinical depression, causing distress and impaired functioning. It should be no surprise that depression is most often observed in persons with advanced stages of cancer, those who have more disability due to cancer, and those experiencing poor pain control. Persons learning that their primary cancer therapy has failed are especially vulnerable, even when there may be additional treatments available for them. If you are experiencing feelings of hopelessness, guilt, and worthlessness, you should tell your family, friends, and healthcare team about these feelings. Both counseling and medication can make a big difference in how you feel and improve symptoms at the same time. Depression is not inevitable for persons coping with cancer. Help is available for anyone living with cancer. (Source: *When the Focus Is on Care: Palliative Care and Cancer, 2005*; American Cancer Society)

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**(Dealing with Prostate Cancer - Continued from page 1)**

Last, but not least, my PSA began to climb again about two years after my surgery. Consultation with my primary care physician, my urologist, and two oncologists led to a regimen of 33 radiation sessions in early 2002. Finally some good news - my post-radiation PSA was undetectable, and it remains so to this day. But nothing is easy. There are side effects to radiation, too. I often experience some slight rectal bleeding during bowel movements, however, reliance on a stool softener has reduced the incidence of bleeding. I have been told that treatment of this condition is problematic, so I am simply living with it.

I have heard that some surgeons say the objectives of the radical prostatectomy (RP) are to get all the cancer, preserve continence, and preserve potency, in that order. Their experience with patients has shown that persistent incontinence is the most bothersome of RP side effects. I struck out on all three objectives! And I can attest to the accuracy of the surgeons' priorities!

I have reviewed the various mechanical and drug alternatives to overcome erectile dysfunction, but I have not pursued any of them. My spouse and I have adjusted to my condition. Incontinence is another story. After my surgery, I required 3-4 pads per day. I soon resorted to the Bard Cunningham penile clamp which reduced my use of pads to one per day. I must wear that "torture device" every waking hour to maintain the one-pad level. Fortunately, I am leak-free (without the clamp) when prone. I have considered the surgically-implanted artificial sphincter to control incontinence, but I am not eager for more surgery. Nevertheless, my daily battle with incontinence is leading me in that direction. Overall, the unfortunate and continuing side effects of both surgery and radiation, I must admit, are getting less tolerable. I would appreciate hearing from men whose experience is similar to mine. Perhaps there is a coping mechanism I am missing.

(**Editor's Note:** If you would like to offer suggestions or comments to the author, you may address them to him at chasnjan@juno.com; address them to the editor who will promptly provide them to the author. My address is at the top of page 2, on the left. Email is OK.)

**WRAMC PROSTATE CANCER SUPPORT GROUP MEETING SCHEDULE**

**Quarterly:** First Wednesday of February, May, August, November; 7:00 PM - 8:30 PM
Joel Auditorium, 2d floor, of the main hospital building
A medical professional presents current topics of interest to the support group

**Monthly:** Second Wednesday of every month; 1:30 PM - 3:00 PM
Second Thursday of every month; 6:30 PM - 8: PM
Both meetings are at the Center for Prostate Disease Research, 5th floor, Ward 56

## PROSTATE CANCER VACCINE TRIALS AT THE NCI

# James L. Gulley, M.D., Ph.D., F.A.C.P.

**Director, Clinical Immunotherapy Group**
**Laboratory of Tumor Immunology and Biology**
**National Cancer Institute, NIH**


**(A summary of a presentation to WRAMC Us TOO on August 3, 2005)**

## INTRODUCTION

It is my pleasure to be here tonight to talk about something near and dear to my heart, that is, how we can influence the body's immune system to help you fight prostate cancer. The general idea is that tumors have escaped the body's normal immune surveillance, therefore, we need to retrain the body's immune system to recognize and attack those tumors.

How do we go about doing that? Well, we must generate an effective vaccine to do the job. First, we need to give the immune system a target that it can use to recognize the prostate cancer and attack it. Then we need to determine how we are going to deliver that target into the immune system in a way that generates a good immune response. Later I will talk about how to further optimize the vaccine. Then we will review applicable clinical trials and some pre-clinical studies.

## FINDING A TARGET

First, let's talk about our choices of a target. I know you are familiar with prostate specific antigen (PSA). PSA is essentially produced only in the prostate, so it is a very good target. In other words, it is not produced in other tissues of the body, so the immune system is not likely to be attacking anything else. If some normal prostate tissue is left behind after radiation or surgery and your cancer is recurring, we can accept the fact that the immune system may attack a few of the normal cells too. After all, the prostate is not a vital organ like the lungs or heart.

PSA is not a good target for antibody-based therapies, but it <u>is</u> a good target for vaccines. Here is why. T-cells are the main part of your immune system that you want activated to help fight the tumor. T-cells can't see whole proteins on the surface of the cancer cells, but they can see anything made in those cells. PSA is made in the prostate and although it is not a cell surface protein, it is a good target for T-cells.

Under laboratory conditions, we took T-cells from patients and stimulated them. Then we took these T-cells and put them in the same well as the prostate cancer cells making PSA. We saw that the T-cells killed the tumor cells that were making PSA, but not the tumor cells that were not making PSA. We knew that if we could train the T-cells to recognize PSA, those T-cells would then be able to kill the tumor.

The body does not give an immune response to normal protein. So we had to find a way to get that PSA into the body to overcome its tolerance to PSA. We developed a unique strategy involving CEA, a different tumor-associated antigen. The mice models that I am showing tonight have a CEA because we have mice that make CEA as part of their

normal tissue. They are tolerant to it much like when we make PSA, we are tolerant to it.

If you take mice that are tolerant to the CEA and give them full CEA protein in an immunologic regimen, the best vaccine that we know how to give with the protein, you see very little, if any, immune response generated. However, if you put that CEA inside a vaccinia virus—we're going to talk about that shortly—you see a very strong immune response generated to the CEA.

## VACCINIA

Now let's talk about vaccinia. Vaccinia is a virus in the same family as smallpox, a virus that causes disease in cows. We're going to talk later about that. Smallpox is a similar virus in the same family that causes disease in birds. We will be talking about both of these viruses this evening. Now I digress briefly from tumor vaccines to talk about the origins of vaccinia.

Time for a history lesson! This slide shows a lesion of vaccinia. In times past when milkmaids milked cows, they would often develop these lesions on their hands which were called milkmaid's nodules. These lesions contained the vaccinia virus. When smallpox raged, these milkmaids were spared from the disease. In 1798, the scientist Edward Jenner vaccinated an eight-year-old boy named James Phipps as an experiment. In effect, he said, "To test the effectiveness of this vaccinia immunization to protect against smallpox, I'm going to give this child this vaccinia, wait several weeks, and then infect him with smallpox. If he gets smallpox and dies, then my theory doesn't work." This 18th century scientific technique obviously would be scandalous in today's scrupulous society, but fortunately, it worked for this child. To prove his point, Jenner gave the boy another dose of smallpox. And, guess what? The boy was immune from the disease. Jenner repeated the procedure on over a hundred patients and published his findings.

This was the origin of the smallpox vaccine. Vaccinia has now been given to over a billion people worldwide and it led to the eradication of smallpox as a common disease. So we now have a very good idea of how to use vaccinia. Thank you, Edward Jenner! And you, too, James Phipps!

How do we make our vaccine? Basically, we take the entire gene from PSA and put it inside the vaccinia virus and then we give it as an injection. When you give it as an injection, these viruses go and infect cells, including the antigen-presenting cells. We refer to these antigen-presenting cells as the "teacher" cells. They are the cells that tell the T-cells what to look for and how to find it. The T-cells then go to the area of the cancer and cause the destruction of the tumor.

Initial studies of this virus, just with vaccinia containing the gene for PSA, showed that it was safe. You could give it to patients with advanced prostate cancer, and then take blood from these patients and it would actually kill tumor cells in a laboratory setting.

We wanted to improve on the immunologic responses that we had and to develop more clinical responses. We simply wanted to optimize the vaccine. So we went back to the laboratory and said, "What can we do? We know we can decrease tolerance, but we are not generating immune responses that cause the rapid shrinkage of tumors in the majority of cases." The first thing we learned was that after multiple applications of vaccinia, the body generated an immune

response that was directed against the vaccinia virus itself, and not against the PSA. So we developed a concept called "Diversified Prime and Boost (DPB)," priming with the vaccinia vector and boosting with an avipox vector such as fowlpox. In animal studies, we showed DPB to be much more effective than giving either vaccinia by itself or fowlpox by itself.

## CLINICAL TRIALS

The Eastern Cooperative Oncology group did a large randomized Phase II study which looked at giving either the fowlpox virus alone before vaccination, or vaccinia first, followed by three fowlpox vaccinations. These were patients who had had rising PSA following surgery or radiation therapy, but they didn't have other signs of recurring disease. None of them had started on hormonal therapy, so we were trying to delay that therapy. And, in fact, it looked as though such therapy could be delayed by giving the vaccinia first, followed by the fowlpox. This study the showed that those patients who got the vaccinia first, followed by the three fowlpox vaccinations had a much longer time than the others before there was PSA progression. The updated data presented at the recent American Society of Clinical Oncology Conference (2005) showed that this procedure could double the time to PSA failure in these patients.

Then we undertook a randomized Phase II trial at the National Cancer Institute (NCI) in patients who had rising PSAs and had been started on hormonal therapy. The patients were randomized to receive vaccine alone (Arm A) or nilutamide (Arm B), which is an anti-antigen, a pill that is used similarly to bilfalutamide (Casodex) or falutamide (Eulixin). There were twenty-one patients in each arm of the study. The median time of treatment failure (defined as either the patient having progressive disease or being unable to tolerate the treatment) indicated that the vaccine appeared to be as good as nilutamide, an already FDA-approved treatment for a patient in this category. We did see patients who had significant declines in their PSAs when getting the vaccine alone.

This slide shows a patient whose PSA was going up quickly; in fact, after the first vaccine, his PSA continued to rise, but then stuttered for a time, before finally dropping precipitously. It was about 17.5 ng/ml here and then dropped to 0.18 ng/ml, staying low for quite a while. This patient was given a vaccine every three months rather than monthly. His PSA did rise again, and he was eventually was taken off the trial after about fourteen months. However, he probably did have clinical benefit from this vaccine.

Here is another patient who was allowed to cross over between the two arms of the study (because he had a rising PSA on the first therapy) and add on the treatment of the other arm. He started out on nilutamide and had a nice decrease in his PSA, but it was relatively short-lived. After starting vaccine, the PSA dropped over 50% and actually remained down for a period of several years, indicating that there was an apparent clinical benefit in this patient with the vaccine.

What can we conclude from this trial? The nilutamide arm did have more patients with declines in their PSAs; however, the declines were relatively short-lived, and the time to treatment failure was similar for both arms. The nilutamide arm also had more toxicities requiring discontinuation of the treatment. There were PSA declines, as

already shown, with just the vaccine alone. The trial showed that the vaccine can work in some people. Can we improve on that response if we combine it with traditional therapies? We will next discuss two trials, one trial where we added vaccine to radiation therapy and another trial where we added it to chemotherapy.

## VACCINES AND RADIATION THERAPY

Patients with localized prostate cancer who are candidates for radiation therapy face a dilemma - up to thirty to forty percent of them, depending on individual risk factors - experience rising PSAs after that treatment. This is often due to the fact that the tumor was already outside of the prostate, but was too small to be seen on the bone scan or CT scan. One potential solution would be to give the radiation therapy plus another systemic therapy, a therapy that can go elsewhere within the body. Vaccines might be effective in dealing with this situation. We have some pre-clinical data from our mice models showing that vaccines and radiation play very nicely together. They work hand-in-hand to help eradicate tumors.

This slide shows how it works. You can see the tumor volume starting out very small and then growing very large over time. This is the vaccine starting on the eighth day, and this is radiation alone starting on the fourteenth day. Tumor growth slowed down, but not very much. Combining the vaccine and radiation therapy produces a synergistic anti-tumor effect—you can see the tumors are growing much more slowly, and four of the ten mice are actually cured of their disease.

We embarked on another randomized Phase II study in which thirty patients with localized or locally advanced prostate cancer, most of them high-risk patients, were randomized to receive either vaccine before, during, and after radiation therapy or no vaccine. There were 19 patients in the first arm and 11 in the second. The vaccine was primed with vaccinia PSA and boosted with fowlpox PSA. In addition to the priming vaccine, we gave one costimulatory molecule called "B7-1." (We're going to come back to the costimulatory molecules in just a second and show why they are so very important). We then took blood from the patients and tested it for the formation of an immune response to PSA. Of the seventeen patients who completed all eight vaccinations, thirteen of them had increases in their PSA-specific T-cells of at least three-fold—a 300% increase in the number of T-cells that could recognize and kill the cancer, whereas none of the patients who had radiation therapy only had a detectable increase in their PSA-specific T-cells. It appeared that the immune response came directly from the vaccine and not from any indirect inflammation caused by the radiation therapy.

The question still remains, "Does this result in tumor-killing?" In order to answer this question definitively, we need a much larger trial and follow-up for a very long time to determine whether or not this procedure has an effect on survival or at least on PSA failure. Nevertheless, we do have some indirect evidence strongly suggesting that there was tumor-associated killing. Certainly we can generate a PSA-specific immune response in the majority of patients undergoing local radiation therapy. Furthermore, there is evidence suggesting immune-mediated killing of prostate cancer cells and the vaccine is well-tolerated when combined with radiation therapy.

## VACCINES AND CHEMOTHERAPY

Now I'd like to discuss the combination of vaccines with chemotherapy. Let's review chemotherapy for prostate cancer. There were twenty-two single agent trials between 1988-1991. No chemotherapy was shown to improve survival in patients with prostate cancer until last year. Docetaxel was then shown to improve survival in men with metastatic prostate cancer by two to three months. We all would like to see that greatly improved, but it's a significant first step.

So we conducted a trial to look at the combination of vaccine with chemotherapy. Has anybody tried this before? Yes. Dr. Liz Jaffey at Johns Hopkins had looked at giving a similar chemotherapy agent, Paclitaxel, which is in the same class as Docetaxel. She had shown that if you give this type of chemotherapy agent with a vaccine, it actually improved not only the anti-tumor response, but it gave improved immune responses as well. Other work done at the National Cancer Institute has shown that this type of chemotherapy was much less likely to damage the T-cells.

Next we took patients with metastatic disease, failed hormone therapy, rising PSA, or with new lesions and randomized them to vaccine with chemotherapy (Arm A) or vaccine alone (Arm B). The idea was to see whether we could generate a good immune response when we combined the vaccine with the chemotherapy. Using this chemotherapy required that we give steroids in order to prevent some of the side effects associated with the chemotherapy. Those steroids also can potentially decrease the immune response.

What we found was that the patients on the vaccine-only arm had exactly the same increase in their number of immune cells as the patients on the vaccine with chemotherapy. So we demonstrated that the vaccine could generate the immune response even when combined with chemotherapy and the comedication steroids, and that the vaccine could be given safely with chemotherapy.

We were still not satisfied with the number of clinical responses. We had to make this vaccine even more potent. So it was back to the laboratory. We came up with T-cell costimulation, which we mentioned earlier and promised to come back to it. Now aware that human T-cell costimulatory molecules not only improve immune responses, but also improve anti-tumor effectiveness in mice, we were able to produce a triad of costimulatory molecules, called "TRICOM." Now this may be more science than you want to know, so suffice to say that that the three molecules bind to different molecules on the surface of the T-cells. Therefore, they are not competing for the same one. Each of these acts through a different "second messenger pathway" to provide a real potential for synergy. Although each gives a slight increase in T-cell activation, acting together they not only improve immune responses, but also anti-tumor effectiveness in mice.

In a study that was just published this year, we also showed that we could get a much more efficient killing of the tumor cell by using these vaccines. The first trials just with vaccinia with the PSA gave a relative killing efficiency of 1. When we used the three costimulatory molecules and the GM-CSF—which we're going to talk about in a moment—we achieved a 850-fold increase in efficiency of killing.

By giving mice a tumor we found that all the mice denied vaccine were dead by ten weeks; of those treated with vaccinia CEA followed by Fowlpox CEA, twenty percent

of the mice were alive long-term; however, with CEA/TRICOM, sixty percent were actually cured of their tumors. So this was definitely considered the best approach, and we were very eager to bring it into the clinic.

Granulocyte Monocyte-Colony Stimulating Factor (GM-CSF) is a growth factor for the white blood cells. It really stimulates the immune system. We administer it at the same site as the vaccination to bring the white blood cells. The result is very similar to the use of TRICOM. The GM-CSF with the TRICOM provided the optimal response.

Next we took the PSA-TRICOM-phased vaccine to a Phase I trial, and the patients had no significant side effects. In the Phase II trial, we put patients on vaccine alone or with GM-CSF. The primary endpoint was to look at which immune response was better—with or without the GM-CSF. Of the 23 evaluable patients in this trial, four have had declines in their PSAs–three of them had declines between thirty and fifty percent, and the fourth had a decline of more than fifty percent. The disease of three of the patients has been stabilized for at least twelve months, while the tumor of one patient shrank. One patient's PSA was rising significantly before starting on vaccine. With the vaccine, his PSA came down very nicely at first, eventually rising again after bouncing around a bit. The PSA of a second patient also came down nicely. I just saw this third patient recently. After thirteen months in the trial his PSA, which came down by 50%, is still stable at about 150.

This is a patient who had an enlarged lymph node, as you can see here. Now note that it virtually goes away following vaccination, and there was a decline in PSA from 85 to 56. This is another patient who had a lymph node. It has not gone away, but it is much smaller and he had a decrease in PSA from 18.8 to 11.6.

We can conclude from this trial that the vaccine is safe with minimal toxicities, basically just redness and some of swelling at the site of injection. Two patients had systemic effects from the vaccine, including fever and muscle aches. Overall, the clinical responses to the vaccine were very meaningful. The four patients who showed clinical evidence of benefit had at least a six-fold increase in the number of T-cells that recognized and attacked the tumor cells.

## SUMMARY

To summarize, these pox vector vaccines appear to be safe. They can generate PSA-specific immune responses, and they appear to be able to kill tumor cells. They cause immunity to targets not found in vaccine in the so-called "antigen cascade." They can cause significant decreases in PSA in some patients and decreases in tumor size in some patients. They can be combined safely with radiation therapy or chemotherapy, and new therapies are being devised that may be even more potent.

In closing, let me mention that there is a considerable research effort to get new therapies for prostate cancer using vaccines. Some of the early results of these other studies are very promising. Two recently opened trials at the NCI include (1) intraprostatic injection of vaccine for patients who have failed radiation, and (2) the addition of anti-CTLA antibody (that takes the brakes of the immune system) to vaccine with metastatic patients.

I would be happy to answer any questions at this time.

## Questions & Answers

**Q:** It appears that the research emphasis is on advanced prostate cancer disease. Why isn't some intervention tried earlier?

**A:** That is a great question. The research stems in large part from the fact that prostate cancer is often indolent. For example, patients who have rising PSAs following surgery, and go untreated, have about eight years before they will develop metastatic disease. If they begin therapy at the first identification of metastatic disease, they will live on average for five more years. The FDA really takes a hard look at clinical endpoints. For Phase III trials, that generally means overall survival. Given the approximately thirteen-year overall median survival of those patients, it is very daunting to conduct trials that are not likely to provide answers for another thirteen years. It greatly increases the cost of the trials.

**Q:** What does CEA stand for?

**A:** It stands for Carcinoma Embryonic Antigen. It is a tumor-associated antigen that is found at high levels in colorectal cancer. It is also found in other cancers, including prostate cancer to a certain degree. About fifteen percent of prostate cancers express CEA, and if you look at patients with metastatic prostate cancer, about half of those patients have elevated CEA levels.

**Q:** What is the ideal animal model for a vaccine?

**A:** The ideal animal model would be one that developed prostate cancer spontaneously. The prostate cancer went primarily to the bones and developed osteoblastic metastasis. It may also go to lymph nodes or liver or lungs, but not as frequently as it goes to bones. The problem we see with the animal models so far is that very few have developed bone metastasis and very few of those developed osteoblastic metastasis. So the researcher must use care in comparing it to the human situation. The other aspect of the ideal animal model for a vaccine would be that it have a target that is tolerant in the host. In other words, the host would think of that as a normal part of the body. What we've done in our mice is to make them CEA transgenic, and we also now have PSA transgenic mice with the PSA as part of their normal system, just as it is in the human.

**Q:** Why does all the research seem to be aimed at men who had radiation therapy?

**A:** The trials are geared to patients with intact prostates who have had radiation therapy or have been on watchful waiting. We give the vaccines directly into the prostate. We do that under ultrasound guidance. We have sought approval from our Institutional Review Board (IRB) to do this type of trial in very high-risk patients before they had surgery in the hope that that we could potentially decrease the number of cancerous cells that were outside the prostate and generate systemic immune responses. The IRB felt it might make the surgery more difficult because of the inflammation that might occur. In the end, we decided to do it in patients who had failed radiation therapy, but who still had intact prostates and biopsy-proven local recurrence.

**Q:** Is salvage radical prostatectomy an option for patients in these trials?

**A:** We have not done any trials with vaccines and salvage radical prostatectomies for patients that failed radiation therapy, and we're not planning to at this time. The trial was designed to take patients who have localized failure and to see what we can do with vaccine therapy to generate an immune response that can hopefully delay the time to initiation of hormonal therapy.

**Q:** Looking way out in the future, do you ever see the day when some idea like this would apply to a true vaccine where a high-risk, fifty-year-old male could get a vaccine and maybe never get prostate cancer?

**A:** That is absolutely where I'd like to see this go. We actually have been talking with our prevention group in the National Cancer Institute, talking about taking men with prostatic interepitheal neoplasia, or PIN. These patients are at significantly higher risk for getting prostate cancer, and there is considerable interest in doing a vaccine trial in that patient population to see if we can prevent them from getting invasive prostate cancer.

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## CENTER FOR PROSTATE DISEASE RESEARCH WEBSITE

Be sure to visit the updated website of the Center for Prostate Disease Research (CPDR) at www.cpdr.org. Read about the CPDR achievements in basic research and clinical research. Use interactive nomograms to predict pathologic outcomes.

The website also features the current issue of the WRAMC Us TOO newsletter; back issues are also available as well.

# ♦ WRAMC US TOO COUNSELORS ♦ (AS OF NOVEMBER 1, 2005)

**(These persons are willing to share their experiences with you. Feel free to call them.)**

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## WATCHFUL WAITING

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## SPOUSE SUPPORT

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**WEDNESDAY, NOVEMBER 2, 2005**
**7 PM**

**JOEL AUDITORIUM (SECOND FLOOR)**
**WALTER REED ARMY MEDICAL CENTER**

## ♦ SPEAKER ♦

**STEVEN J. TULIN, Ph.D**
**Clinical Psychologist, Department of Psychology**
**Walter Reed Army Medical Center**

## ♦ TOPIC ♦

**"PSYCHOLOGICAL FACTORS IN HELPING MEN WITH PROSTATE CANCER"**