



PROSTATE CANCER *HOT SHEET*

Us Too! INTERNATIONAL

NOVEMBER 2002

REPORT FROM THE NINTH ANNUAL CaP CURE SCIENTIFIC RETREAT

**William "Bill" Blair
Chair, Scientific Advisory Panel
Us Too! International.**

I recently attended the Ninth Annual CaP CURE Scientific Retreat held in Wash. DC on Sept 20-22, as a representative from *Us Too!*. This was an outstanding meeting that covered all areas of interest in prostate cancer. There were approximately 270 attendees with half that number coming from the scientific/clinical community, and the other half from industry, law, government agencies, support groups, etc.

Topics discussed covered basic science, clinical trials, epidemiology, accelerating medical research [panel], prevention, diagnostic testing, challenge of curing cancer [panel], alternative therapies, and dietary interventions. There were 39 presentations and over 80 posters related to prostate cancer.

Many government officials participated in panel discussions moderated by Michael Milkin [founder of CaP CURE]: Andrew Von Eschenbach, Director, NCI, Eve Slater Assistant Secretary of Health, and Richard Pazdur, FDA. Industry was also well represented for the panel discussions: Jeff Leiden from Abbott Labs, David Parker from Novartis, and William Berg of Aventis.

I have confined comments which follow to a few observations on subjects of medical interest to prostate cancer:

- A study from the Hebrew University, Israel demonstrated that androgen deprivation increased skeletal bone loss and increased bone metastasis when the very aggressive prostate cancer PC-3 [androgen independent] was injected into laboratory animals. Treatment with

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GENE MIGHT FLAG LETHAL PROSTATE CANCER

**Lidia Wasowicz
UPI Senior Science Writer
UPI - October 10, 2002**

Experiments with tissue samples taken from men who died of prostate cancer that had spread to their other organs might point to ways to detect — and target — the malignancy early enough to save lives, scientists said.

The research unfurled a potential red flag for metastatic, or spreading, prostate cancer. Using state-of-the-art technologies, tissue analyses revealed levels of a protein called EZH2 appear to rise as the disease heads into the final, fatal stage.

"We found the greatest EZH2 overexpression in metastatic prostate cancer tissue," said Dr. Arul Chinnaiyan, assistant professor of pathology and urology at the University of Michigan Medical School in Ann Arbor and lead author of the study published in the Oct. 10 issue of the British journal *Nature*.

"At this point, it's unclear whether the gene (that expresses EZH2) plays a role in cancer's development or is simply an indicator of lethal progression."

The findings imply a future diagnostic test for high EZH2 levels might provide a warning of metastatic prostate cancer and identify patients who would benefit most from aggressive treatment, including prostate-removing surgery and radiation therapy, that could prolong their lives, said the investigators from the U-M Comprehensive Cancer Center.

Further analysis revealed during the progression of disease, EZH2 might silence a constellation of genes, including some assigned to suppress tumors.

"(The authors) report that when the EZH2

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MEN MUST FORGET EGOS AND GET CHECKUPS FOR LASTING HEALTH

**By Willie Mickell
U-WIRE - Northern Illinois Univ.**

Some men are willing to fight a man over a parking space and risk receiving cuts and bruises. Most men, though, are terrified of walking into that one entrance room with one table, one chair and one bed to be seen by a doctor.

According to health experts, men are dying at a faster rate than women because they don't go to the doctor. The health gap between men and women is widening. The average white male is dying six years before white women. The average black male is dying 12 years before black women. Experts say that the cause is not genetic and that it is due to a lack of proper health care and treatment that men die sooner than women.

It's unfortunate that in our society, men have been taught to deal with pain different than women. While women are more likely to have regular checkups at the doctor, men try to be tough and deal with their pain by hoping it will go away. Men shouldn't put themselves in a situation to suffer longer and become more sick than they have to.

A man who behaves in this manner is not a real man. A real man would go to the doctor when he is in pain or for regular checkups. Experts say that one reason that a lot of men don't go to the doctor is because they are scared of the results and they are scared of being seen by a male doctor.

Men who won't go to the doctor for regular checkups must remember they can either go to the doctor for regular checkups now and be treated, or they can rush themselves to death and be examined by

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PROSTATE CANCER NEWS YOU CAN USE

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LESS INVASIVE, MORE QUESTIONS: EXPERTS DEBATE THE BENEFITS OF LAPAROSCOPIC PROSTATE SURGERY
WashingtonPost.com - Oct 15, 2002
 Men can decide to have their prostates removed laparoscopically, a new and much debated surgical procedure that promises to dramatically reduce pain, blood loss and the month-long convalescence typically associated with the standard operation. Instead of a single five- to 10-inch abdominal incision, the surgeon makes five half-inch cuts called ports. Fine instruments including a tiny video camera are threaded through these ports and are used to perform the surgery. The prostate is extracted through the middle port.

SCREENING FOR PROSTATE CANCER IN HIGH RISK POPULATIONS
The Journal of Urology 2002; 168(5):1980-1984

Black men and men with a family history of prostate cancer are at a 75% to 80% higher risk for prostate cancer. On initial screening of high risk men in their fourth decade only 8% have positive screening tests; however, approximately 55% of these men have tumors, most of which are medically important with favorable prognostic features.

EFFECT OF NONSTEROIDAL ANTI-INFLAMMATORY AGENTS AND FINASTERIDE ON PROSTATE CANCER RISK
The Journal of Urology 2002; 168(5):1985-1988

The results suggest that finasteride could have a chemopreventive role in prostate cancer. While aspirin did not show any impact on prostate cancer risk, the role of nonaspirin nonsteroidal anti-inflammatory drugs warrants further studies.

THE ACCURACY OF THE INCREASED PSA LEVEL (>= 20 NG./ML.) IN PREDICTING PCA: IS BIOPSY ALWAYS REQUIRED?
The Journal of Urology 2002; 168(5):1990-1993

Serum PSA, when increased above 50 ng/ml., is 98.5% accurate in predicting the presence of PCA on tissue biopsy. Nonetheless, since transrectal prostate biopsy has a low complication rate and is relatively well tolerated, we recommend continuing to biopsy most patients with high PSA levels. However, carefully selected elderly patients on chronic anticoagulation, with severe comorbidities or presenting with spinal cord compression may not require biopsy before androgen ablative therapy since PSA is highly accurate in diagnosing PCA at levels greater than 50 ng./ml.

PERCENTAGE OF POSITIVE BIOPSY CORES AS PREDICTOR OF CLINICAL OUTCOME IN PROSTATE CANCER TREATED WITH RADIOTHERAPY

The Journal of Urology 2002; 168(5):1994-1999

Percent positive pretreatment biopsy cores is a powerful predictor of biochemical and clinical outcome for prostate cancer treated with radiotherapy, independent of other known prognostic factors. Percent positive cores should be seriously considered as a primary factor in risk group stratification for prostate cancer.

PSA RESPONSE TO FINASTERIDE CHALLENGE IN MEN WITH A SERUM PSA GREATER THAN 4 NG/ML AND PREVIOUS NEGATIVE PROSTATE BIOPSY
UROLOGY - Volume 60 Issue 3 (September 2002) Pages 464-468

The data in this preliminary study suggest that the magnitude of change in serum PSA after 1 year of finasteride challenge may be useful in diagnosing CaP in patients with elevated PSA levels and prior negative prostate biopsy

HEART DISEASE GENE LINK FOUND
 Researchers at Johns Hopkins, Wake Forest, and the National Human Genome Research Institute have implicated mutations in a "heart disease gene" in hereditary prostate cancer. The findings, which offer new evidence that at least some cases of prostate cancer may begin with an infection and inflammatory response, were published online September 16, 2002, in Nature Genetics.

TUMORS SMALLER, VESSELS FEWER WHEN TREATED WITH ANTISENSE HYALURONAN
 Prostate cancer cells lacking the ability to secrete hyaluronan generate smaller tumors and less neovascularization than do those that can secrete hyaluronan. As a result, medical investigators think that restricting hyaluronan could have the effect of controlling tumor kinetics such as proliferation and angiogenesis.

PSA PREDICTS FUTURE FOR PROSTATE CANCER PATIENTS
 Measuring prostate-specific antigen (PSA) levels in men five years after they receive radiation treatment for prostate cancer helps predict their chances for survival for several years. That's the finding of a new study in the October International Journal of Radiation Oncology. Men who have very low PSA levels at the five-year mark have low odds of suffering a relapse of prostate cancer at 10 years and beyond, the study says.

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**PSA BOUNCE PHENOMENON AFTER
 EXTERNAL BEAM RADIATION FOR
 CLINICALLY LOCALIZED PCA**
The Journal of Urology 2002;
168(5):2001-2005

Of men with prostate cancer treated with external beam radiation therapy 12% experienced a transient increase in PSA (PSA bounce) followed by a return to pre-bounce levels after radiation. The PSA bounce phenomenon was not predictive of time to biochemical recurrence.

**NEOADJUVANT THERAPY BEFORE
 RADICAL PROSTATECTOMY FOR
 CLINICAL T3/T4 PCA: 5-YEAR
 FOLLOWUP, PHASE II SOUTHWEST
 ONCOLOGY GROUP STUDY 9109**
The Journal of Urology 2002;
168(5):2016-2019

Neoadjuvant hormonal therapy followed by radical prostatectomy is reasonable and appropriate for clinical stage T3 prostate cancer. A progression-free and overall 5-year survival of 70% and 90%, respectively, compares favorably to Radiation Therapy Oncology Group neoadjuvant trial outcomes for this stage of prostate cancer.

**SERUM LEVELS OF INSULIN-LIKE
 GROWTH FACTOR-1 AND INSULIN-LIKE
 GROWTH FACTOR-1 BINDING PROTEINS
 AFTER RADICAL PROSTATECTOMY**
The Journal of Urology 2002;
168(5):2249-2252

Increased levels of IGF-1 and IGF-1 binding proteins were unexpected after prostatectomy. This result makes it extremely unlikely that secretion from the prostate, even if it contains cancer, affects serum levels of these proteins. The implication of these findings is that endocrine production of IGF-1 is a factor in prostate cancer risk. Therefore, strategies to lower serum IGF-1 may be potentially useful.

**THE PROSPECTS OF RETINOIDS IN THE
 TREATMENT OF PROSTATE CANCER**
Anti-Cancer Drugs 2002;
13(8):781-790

Aggressive, androgen-independent, metastatic prostate cancer is incurable, and the search for new therapies has been directed towards identifying agents that block proliferation and induce differentiation and/or apoptosis of prostate cancer cells. Retinoid receptor agonists, such as all-trans retinoic acid, can induce apoptosis of PCa cells, but clinical studies have demonstrated only mild to moderate efficacy. Retinoic acid receptor antagonists are a new class of retinoids, and pre-clinical studies have shown that

they potently inhibit the growth of prostate cancer cells and induce apoptosis.

**ENHANCED RADIATION SENSITIVITY IN
 PCA BY INHIBITION OF THE CELL
 SURVIVAL PROTEIN CLUSTERIN**
Clin Cancer Res 2002 Oct;
8(10):3276-84

Findings support the hypothesis that clusterin acts as a cell survival protein that mediates radioresistance through the inhibition of apoptosis. In vivo results further suggest that inactivation of clusterin using ASO technology might offer a novel strategy to improve results of radiation therapy for prostate cancer patients.

**A RANDOMIZED, PLACEBO-CONTROLLED
 TRIAL OF ZOLEDRONIC ACID IN PATIENTS
 WITH HORMONE-REFRACTORY
 METASTATIC PROSTATE CARCINOMA**
*Journal of the National Cancer
 Institute, Vol. 94, No. 19, 1458-1468,*
October 2, 2002

Zoledronic acid at 4 mg reduced skeletal-related events in prostate cancer patients with bone metastases

**SUPERIOR EFFECTIVENESS OF IBUPROFEN
 COMPARED WITH OTHER NSAIDS FOR
 REDUCING THE SURVIVAL OF HUMAN
 PROSTATE CANCER CELLS**
Cancer Chemother Pharmacol (2002)
50: 277-284

Observations support the use of ibuprofen in future in vivo studies and in clinical trials designed to test the effectiveness of NSAIDs against human prostate cancer.

**OBESITY DURING YOUTH INCREASES
 RISK OF CANCER MORTALITY AT
 OLDER AGE**

Research in The Journal of Epidemiology and Community Health shows that young adults with obesity problems have a greater chance of dying from cancer compared with thinner people.

**PATIENTS WITH METASTATIC HORMONE-
 RESISTANT PROSTATE CANCER BENEFIT
 FROM WEEKLY EPIRUBICIN THERAPY**
Brit J Cancer 2002;87:720-5

Weekly administration of epirubicin chemotherapy may have swift and lasting palliative results and may positively effect quality of life (QoL) and survival for patients with metastatic hormone-resistant prostate cancer (HRPC), research shows. Overall, the therapy was well tolerated. Researchers observed grade 3 neutropenia in 8% of the patients, grade 3 anemia in 7% of patients, and grade 3 thrombocytopenia in 3% of the patients.

**PROSPECTIVE RANDOMISED TRIAL
 COMPARING DIETHYLSTILBOESTROL AND
 FLUTAMIDE IN THE TREATMENT OF
 HORMONE RELEASED PROSTATE CANCER**
International Journal of Urology -
Volume 9 Issue 8 Page 431
August 2002

In HRPC, treatment with stilboestrol is associated with a greater PSA fall and an increase in median survival when compared to flutamide treatment.

**CANCER TREATMENT LESSENS CHANCE
 OF SIDE EFFECTS**
Ft Worth Star Telegram - Sept 30 '02

Doctors are testing a more precise radiation beam to treat prostate cancer with far less damage to nearby healthy cells and potentially decreasing the chance of side effects such as impotence, according to a report in the Orlando Sentinel. The machine is called the Novalis Shaped Beam Surgery system, which is based on an existing radiation approach called intensity modulated radiation therapy, or IMRT.

**EMERGING ROLE OF ADJUVANT
 HORMONAL THERAPY**
Urology 2002 Sep;60(3 Suppl 1)
13-20; discussion 21

Recent years have seen a downward shift in the most common disease stage at diagnosis and in the age of patients diagnosed with prostate cancer. Although younger men with clinically localized disease are generally offered radiotherapy or radical prostatectomy, such treatment does not always produce a cure. Adjuvant hormonal therapy (medical or surgical castration) has been shown to extend progression-free survival in both the radiotherapy and surgical settings, and overall survival benefits have also been demonstrated in some studies. However, castration is associated with sexual dysfunction that may be unacceptable, particularly among younger patients.

**THE ROLE OF ANDROGEN DEPRIVATION
 THERAPY COMBINED WITH PROSTATE
 BRACHYTHERAPY**
Urology 2002 Sep;60(3 Suppl 1):
39-44; discussion 44

Several prospective randomized clinical trials have demonstrated improved outcomes in men receiving androgen deprivation therapy (ADT) in combination with definitive local therapy (external-beam radiotherapy or surgery). ADT is commonly combined with prostate brachytherapy (PB) to "downsize" the prostate gland. No substantial effects of ADT on disease-free

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NEWS YOU CAN USE

(continued from page 3)

survival are apparent. Prospective randomized trials of PB and ADT are required.

ANTIANDROGEN MONOTHERAPY: INDICATIONS AND RESULTS

Urology 2002 Sep;60(3 Suppl 1):64-71

Many patients with prostate cancer for whom hormonal therapy is indicated are still physically and sexually active; quality of life is therefore a vital issue when considering treatment options. Traditional castration-based therapies, although effective, have implications with respect to quality of life, causing loss of libido, impotence, fatigue, and reduced bone mineral density. Monotherapy with a nonsteroidal antiandrogen is an attractive therapeutic alternative to castration, offering effective therapy with potential quality-of-life benefits. Of the available nonsteroidal antiandrogens, bicalutamide has been most extensively evaluated in the monotherapy setting. Mature combined data (56% mortality) from 2 large randomized studies show no statistically significant difference in overall survival between bicalutamide 150-mg monotherapy and castration in patients with locally advanced, nonmetastatic (stage M0) disease. Survival outcome in patients with metastatic (stage M1) disease (43% mortality) favored castration, although the difference in median survival between the groups was only 6 weeks. Bicalutamide 150-mg monotherapy was associated with significant advantages compared with castration, in terms of sexual interest and physical capacity, in patients with either M0 and M1 stage disease. Data from a small subgroup of patients with stage M0 disease suggest that bicalutamide may also reduce the risk of osteoporosis compared with castration. Long-term therapy with bicalutamide 150-mg monotherapy is generally well tolerated, with a predictable side-effect profile. The most common side effects are male breast pain and gynecomastia. Emerging evidence also supports the use of bicalutamide 150 mg, both as immediate monotherapy and as adjuvant therapy in early stage (localized or locally advanced) prostate cancer.

PROGNOSTIC VALUE OF BONE SCAN IN PATIENTS WITH METASTATIC PROSTATE CANCER TREATED INITIALLY WITH ANDROGEN DEPRIVATION THERAPY

J Urol 2002 Oct;168(4):1423-1426

Classifying bone scans according to the site of metastases (axial versus

appendicular) had many advantages. It is easy to understand and helps urologist better predict the patient prognosis. Axial metastases carries a better prognosis than appendicular metastasis.

PHOTODYNAMIC THERAPY FOR PROSTATE CANCER RECURRENCE AFTER

RADIOTHERAPY: A PHASE I STUDY

J Urol 2002 Oct;168(4):1427-1432

Photodynamic therapy is a new option that could be suitable for organ confined prostate cancer recurrence after radiotherapy. With more precise light dosimetry, it may be possible to destroy essentially all glandular tissue within the prostate with few complications. These results suggest that photodynamic therapy merits further investigation.

LONG-TERM DURABILITY OF PSA FAILURE-FREE SURVIVAL AFTER RADIOTHERAPY FOR LOCALIZED PROSTATE CANCER

Int J Radiat Oncol Biol Phys 2002 Oct 1;54(2):420

When PSA levels remain low (<2 ng/mL) 5 years after EBRT, the great majority of patients will be biochemically disease free at 10 years. The hazard rates of biochemical progression in the 6-10 years after treatment are low and are comparable to those published for prostatectomy series.

CONTROVERSIES IN THE SYSTEMIC MANAGEMENT OF PATIENTS WITH EVIDENCE OF BIOCHEMICAL FAILURE FOLLOWING RADICAL PROSTATECTOMY

Cancer Treatment Reviews; p 189-194, Volume 28, Number 4, August 2002

The management of patients with evidence of a detectable prostate-specific antigen (PSA) following prostatectomy is an increasingly common and difficult issue for patients and clinicians alike. In the setting in which biochemical failure is believed representative of early systemic failure, therapeutic options primarily involve the use of hormonal therapy. Extrapolating results of early vs. delayed hormonal therapy from studies of patients with more advanced prostate cancer is problematic. Antiandrogen monotherapy and intermittent androgen deprivation are increasingly popular approaches, although their ultimate utility remains unproven. This patient subset is an optimal one in which to conduct clinical trials to both define the role of hormonal therapy and to investigate novel, non-hormonal approaches. The most appropriate therapeutic intervention for patients with evidence of biochemical failure following

radical prostatectomy remains undefined.

HIGH-FREQUENCY DOPPLER US IMAGING FOR PROSTATE CANCER DETECTION

Radiology 2002;225:71-77

Targeted biopsy performed on the basis of high-frequency color or power doppler findings will miss a substantial number of cancers detected with sextant biopsy.

LABORATORY STUDY EXPLAINS CLINICAL PROMISE OF

ANTIANGIOGENESIS CANCER DRUG

For nearly 5 years, doctors at the University of Michigan Comprehensive Cancer Center have noted promising cancer-slowng results from early clinical trials of a drug that lowers the level of copper in cancer patients' blood. Now, new U-M laboratory research results are telling them exactly how that experimental drug works, and showing them its cancer-fighting potential on a cellular level. The findings, published in Cancer Research, have implications for the approach to cancer treatment known as antiangiogenesis. The paper describes how the drug - tetrathiomolybdate, or TM - keeps tumor cells from sending signals that spur the formation of new blood vessels. By keeping copper low and blocking the NFkB signaling pathway, the researchers believe, TM blocks the angiogenesis that lets cancer grow and spread.

ATHEROSCLEROSIS GENE INCREASES SUSCEPTIBILITY TO PROSTATE CANCER

The LANCET - Volume 360, Issue 9337, Pages 928

The macrophage scavenger receptor 1 gene (MSR1), which predisposes to atherosclerotic plaque formation in arteries, has been implicated in non-hereditary prostate cancer in a study published this week. William Isaacs (Johns Hopkins Medical Institutions, Baltimore, MD, USA), Jianfeng Xu (Wake Forest University, Winston-Salem, NC, USA), and colleagues identified seven specific mutations in the MSR1 gene that are associated with prostate cancer in men of both African American and European descent.

PSA CUTOFF OF 2.6 NG/ML FOR PROSTATE CANCER SCREENING IS ASSOCIATED WITH FAVORABLE PATHOLOGIC TUMOR FEATURES

UROLOGY - Volume 60 Issue 3 (September 2002) Pages 469-473

The use of a 2.6-ng/mL PSA threshold (continued on page 8)

ERECTILE DYSFUNCTION UPDATES

FAINING RISK WITH VIAGRA, BLOOD-PRESSURE DRUGS LABEL WARNS AGAINST TAKING BOTH WITHIN A FOUR-HOUR PERIOD

USA TODAY - September 26, 2002

Taking Viagra within four hours of taking an alpha-blocker, a group of drugs used to treat high blood pressure and enlarged prostates, could cause fainting, according to a new precaution listed on the impotence pill's label. Viagra itself lowers blood pressure. Since it came on the market 4 years ago, its label has warned that men on any nitrate drug, such as nitroglycerin, should never take Viagra because their blood pressure could drop dangerously low.

LEVITRA MAY BE SUCCESSFUL RIVAL FOR VIAGRA IN TREATING ERECTILE DYSFUNCTION

Bayer AG and GlaxoSmithKline Plc's Levitra (vardenafil), a potential rival for Pfizer Inc.'s Viagra (sildenafil), has demonstrated promising results in several clinical studies, according to data released by Bayer and GSK. A study presented in Montreal, Canada, at the World Congress of the International Society for Sexual and Impotence Research assessed 805 men with erectile dysfunction. After 12 weeks of treatment, as much as 71 percent of patients who had undergone prostatectomy demonstrated a statistically significant improvement in erections as compared with 12 percent of men on placebo. In addition, a small subset of patients experienced a significant decrease in depressive symptoms in prostatectomy patients.

A DOUBLE-BLIND CROSSOVER STUDY EVALUATING THE EFFICACY OF KOREAN RED GINSENG IN PATIENTS WITH ERECTILE DYSFUNCTION: A PRELIMINARY REPORT

The Journal of Urology 2002; 168(5):2070-2073

Data show that Korean red ginseng can be an effective alternative for treating male erectile dysfunction.

NEW STRATEGIES IMPROVE SUCCESS OF ORAL ED THERAPY

Urology Times - October 1, 2002

Men with erectile dysfunction who fail initial treatment with sildenafil citrate (Viagra) are seeing varying degrees of improvement when therapy is supplemented with other agents, vacuum devices, or education and counselling.

PSYCHOLOGICAL IMPACT OF ERECTILE DYSFUNCTION: VALIDATION OF A NEW HEALTH RELATED QUALITY OF LIFE MEASURE FOR PATIENTS WITH ERECTILE DYSFUNCTION

Two new scales were developed to measure the psychological impact of erectile dysfunction and they showed good reliability and validity. These new scales, named the Psychological Impact of Erectile Dysfunction instrument, comprehensively capture the psychological effect of erectile dysfunction on health related quality of life, which is not adequately assessed by existing patient centered measures of erectile function.

PATIENT REPORTED SEXUAL FUNCTION FOLLOWING LAPAROSCOPIC RADICAL PROSTATECTOMY
The Journal of Urology 2002; 168(5):2078-2082

The overall rate of patients who had erections preoperatively and maintained erections after surgery (53.8%) is comparable to the results for open surgery. Patients with bilateral preservation did better than those with unilateral preservation. Preliminary results show a promising rate of potency at 1 year after laparoscopic radical prostatectomy.

DEFINING SEXUAL OUTCOMES AFTER TREATMENT FOR LOCALIZED PROSTATE CARCINOMA
Cancer - Volume 95, Issue 8, 2002.
Pages: 1773-1785

The great majority of men who survive prostate carcinoma do not achieve a return to functional sexual activity in the years after treatment. The priorities a man places on sexuality and on having a sexually functional partner are important factors in sexual satisfaction at follow-up, over and above the influence of age and medical factors.

NEW TITAN™ PENILE IMPLANT DESIGNED FOR MEN WITH DRUG RESISTANT ERECTILE DYSFUNCTION LAUNCHED AT THE INTERNATIONAL SOCIETY FOR SEXUAL AND IMPOTENCE RESEARCH IN MONTREAL

Over 10 Million Men Unresponsive to Viagra(r) and Other Drugs Can Now Treat Their Erectile Dysfunction — A new penile implant designed to treat men living with drug resistant Erectile Dysfunction (DRED) was introduced in Montreal to doctors attending the 10th World Congress of the International Society for Sexual and Impotence Research (ISSIR). The Titan Penile Implant™,

manufactured by Mentor Corporation of Santa Barbara, CA

GUILFORD PHARMACEUTICALS REPORTS POSITIVE RESULTS WITH NEUROIMMUNOPHILIN LIGANDS IN MODELS OF POST-PROSTATECTOMY ERECTILE DYSFUNCTION

Guilford Pharmaceuticals Inc. announced that its novel neuroimmunophilin ligand, GPI 1485, has demonstrated substantial neuroprotective and neuroregenerative activity in preclinical models of post-prostatectomy erectile dysfunction. Neuroimmunophilin ligands are orally administered drugs which have shown an ability to promote the regeneration and protection of both central and peripheral nerves. The researchers concluded that treatment with FK506, or other neuroimmunophilin ligands, may offer significant neuroprotection, and enhance preservation of penile innervation and erectile function following radical prostate surgery.

ERECTILE DYSFUNCTION: ASK THE EXPERT

SIDE EFFECTS OF TRIMIX THERAPY
Medscape Urology 4(2), 2002

Question: I have a patient who is using Triple P as intercavernosal injection for erectile dysfunction. He found an article describing possible side effects (not Peyronie's) such as scarring and fibrosis. Is there evidence or concern for this outcome?

Response from Wayne J. G. Hellstrom, MD, FACS, 09/25/2002:

Over the past 2 decades, self-injection therapy has proven to be both safe and efficacious, and is considered the best second-line drug therapy for the management of erectile dysfunction. The 3 vasoactive agents commonly used alone or in combination are papaverine, phentolamine, and prostaglandin E1 (PGE1 alprostadil). PGE1 (Edex/Viridal; Schwarz Pharma; Monheim, Germany, or Caverject; Pharmacia Corporation; Peapack, New Jersey) is the most widely used vasoactive agent because it is FDA-approved and the most researched. In the event of pain, which occurs in 30% of patients taking PGE1, or inadequate penile rigidity, clinicians may resort to off-label synergistic combinations, such as papaverine and phentolamine (bimix), or papaverine, phentolamine, and PGE1 (trimix). Fibrotic reactions with intracavernous injection therapy have been observed since the early 1980s. A

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GENE FLAG FOR PCA

(continued from page 1)

gene is activated in prostate cancer cells, a substantial number of other genes are shut down,” said Bruce Zetter and Jacqueline Banyard of Children’s Hospital in Boston, who analyzed the findings in a commentary.

“If some of the products of these genes suppress tumor development, their repression by EZH2 could accelerate a tumor’s progress towards metastasis.”

If that is the case — which the scientists think likely — the protein could serve as a therapeutic target, they said.

“This is a fabulous scientific finding,” Zetter, who is also professor of cancer biology at Harvard Medical School, told United Press International. “It’s one that’s going to make people who study metastasis take a new view of how the process works, and it’s going to give us new insights into how tumors actually metastasize.”

It will take additional time and testing before patients might benefit from the work, Zetter cautioned. “This is still a research tool,” he said.

Cancer begins when, for little-understood reasons, a normal cell turns aberrant. In the prostate gland — a chestnut-sized organ at the base of the bladder that maintains proper function of the male reproductive tract — timid tumor cells can acquire malignant aggressiveness in a complex process that spans years, even decades. As the body’s lines of defense — including control of cancer-related genes that can swiftly switch on or off — fall by the wayside, the malignancy gains momentum.

Buoyed by a series of mutations that infuse them with increasing pugnacity, the wayward cells march through several phases, from the benign, when they cause no harm, to the invasive, when they start making trouble, to the metastatic, when they spread dangerously to distant organs, to the lethal, when they become unstoppable.

At the moment, doctors have no way to determine accurately which patients will follow which course. “With the existing markers, it is difficult to predict whether a clinically detected prostate cancer will progress,” Chinnaiyan told UPI.

The new study, the first to link EZH2 to

solid tumors, suggests physicians might be able to make such a potentially life-saving distinction by gauging the protein’s levels.

“Over the past 50 years, there has been no significant improvement in clinical outcome for men diagnosed with advanced prostate cancer and no way to tell ahead of time which cancers will spread and which cancers will remain localized,” said Mark Rubin, now an associate professor of pathology at Brigham and Women’s Hospital and director of the Dana Farber Harvard Cancer Center Tissue Microarray Core in Boston.

“It is exciting to think that we may have finally found something to help the 30,000 men who die every year from metastatic prostate cancer.”

An estimated 189,000 men will be diagnosed with PCa and some 30,200 will die of the disease in the United States this year. Only lung cancer is a greater cancer killer of US men. Worldwide, PCa is the sixth most common malignancy, touching an estimated 30 percent of men over 50. Reported prevalence varies greatly around the globe. As an example, the U.S. PCa rate is 120 times higher than China’s.

That may be due, in part, to Americans’ widespread use of screening techniques such as the PSA test, which measures the amount of prostate-specific antigen — a prostate-produced protein — in the blood. High levels could indicate cancer, although often they also portend a benign condition called prostatic hyperplasia — an enlarged prostate. High PSA also could indicate prostatitis, an inflammation of the gland. Both are treatable conditions common among older men. In fact, two-thirds of men with elevated PSA do not have prostate cancer.

By the same token, low PSA levels do not necessarily point to a clean bill of health, with a quarter of men with a cancerous prostate getting a normal reading.

Such uncertainties prompted scientists to voice concern at the 2001 European Cancer Conference in Lisbon that widespread introduction of the PSA test could lead to unnecessary, risky operations.

Extensive screening — the cancer society recommends an annual PSA test starting at age 50 and earlier in high-risk groups — has improved detection of prostate

malignancy significantly. Even though many of the cancers are slow-growing tumors in the elderly that pose little threat to life, a large number of men opt for treatment that can leave them impotent, incontinent or both.

The other option — “watchful waiting” — entails checkups every few months to see whether the tumor is aggressive enough to warrant prostate removal or radiotherapy.

“It is now hard to tell which patients should be observed by watchful waiting and which should be treated with surgery and radiation,” Zetter said.

Scientists hope future tests based on EZH2 and other cancer biomarkers will ease the problem.

In their experiments, the investigators found the EZH2-based crystal ball of disease progression was significantly more accurate than such staples of prediction as PSA, which indicates how much cancer is present; the Gleason score, which indicates how fast the cancer is growing; and tumor stage, which indicates where the cancer is located.

EZH2’s cancer connection emerged in studies comparing 1,000 tissue samples ranging from normal to lethally cancerous. Of these, 400 came from patients who died from hormone-refractory metastatic prostate cancer, advanced disease that despite hormone treatment regroups and returns with a deadly vengeance.

To glean an overall genetic picture of EZH2’s machinations, the researchers relied on new DNA microarray technology that is reshaping molecular biology by enabling investigators to monitor the complex interactions among thousands of genes simultaneously.

The analysis showed EZH2 repressed 163 genes in tissue with early prostate cancer. When the protein was restrained, the scientists noted a dramatic drop in cancer cell growth.

“Results provide new insight into the role of one particular protein, EZH2, in tumor biology and in so doing reveal a potential new mechanism underlying tumor progression” said Zetter and Banyard.

Concluded Chinnaiyan, “This work will lay the foundation for the discovery of novel diagnostic and prognostic markers as well as therapeutic targets for this common disease.”

CAP CURE

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Zoledronic acid inhibited bone loss, bone metastasis, and prolonged survival. These experimental observations support the view that pre-emptive use of Bisphosphonates [Zoledronic acid] may prevent bone metastasis in aggressive prostate cancer.

- Pro PSA is a newly developed test to detect prostate cancer with a low serum PSA, ie.2.5-4 ug.ml. Pro [precursor] PSA is a unique form of PSA that is highly associated with prostate cancer where as free and conjugated PSA shows little or no diagnostic value for 2.5-4 PSA values.
- The effect of a non-antibiotic Tetracycline on metastasis of prostate cancer was studied. The compound CMT-3 inhibits proliferation of prostate cancer cells, blocks MMPs [Metalloproteinase], reduced the incidence of bone metastasis by 80%, and increased survival in laboratory rats injected with prostate cancer cells. This drug is currently in Phase I and II clinical trials which means it may become available for widespread use in the near future!
- A preclinical trial evaluated the effect of Doxorubicin laden thermostable liposome [fat globules] on solid tumors. The Doxorubicin/Liposome moiety is injected intravenously and heat is applied externally over the area [tumor] to be treated. This causes the release of the chemotherapy at the defined target sparing normal tissue from toxicity. Experimentally this treatment caused complete regression in 11 of 11 tumors. A Phase 1 human trial will start this October at Roswell Park.
- The effect of Halofunginone a specific inhibitor of Collagen Type 1 synthesis was tested on several human prostate cancers in vitro. Halofunginone inhibits PSA and prostate cancer growth. Of particular interest is that this compound completely inhibits PC-22 a neuroendocrine small cell carcinoma for which there is no definitive treatment and is invariably fatal. In addition Halofunginone inhibits blood vessel growth. This drug is currently approved by the FDA for veterinary use and has a "special use" for Scleroderma. A Phase 1 trial has been done and found to be safe and well tolerated at therapeutic dose levels. This very exciting drug may

be in clinical use in the near future.

This is a very brief first impression and I hope it reveals my enthusiasms for CaP CURE as an organization that is focused on the needs of prostate cancer patients emphasizing translation from the laboratory to the patient.

I will be writing a complete report on the scientific presentations from the CaP CURE retreat in the near future.

OTHER ANNOUNCEMENTS FROM THE 2002 CaP CURE SCIENTIFIC RETREAT

ATRIX PRESENTS RESEARCH RESULTS FOR FOUR-MONTH PROSTATE CANCER PRODUCT PR Newswire - Sept. 26, 2002

Atrix Laboratories, Inc. announced Phase III clinical results for the company's Eligard(TM) 30mg (leuprolide acetate for injectible suspension) prostate cancer treatment. "Participants focused on the unique attributes of the Atrigel(R) drug delivery system used in the Eligard products. Most were interested in the small volume of the injection and the data which shows that Atrigel can consistently deliver sustained-levels of leuprolide acetate for four months. They also expressed excitement about a potential new option in treatment for advanced prostate cancer." said Dr. Stephen Warren, vice president of research and development. Eligard 30 mg, in the Atrigel(R) drug delivery technology was developed to deliver leuprolide acetate over four months to lower testosterone levels in men with advanced prostate cancer. Independent studies have shown that Atrix received approvals from the FDA for its Eligard 7.5mg one-month product and Eligard 22.5mg three-month product in January and July 2002, respectively.

DENDREON ANNOUNCES PROMISING PROVENGE PHASE III CLINICAL TRIAL RESULTS WHICH DEMONSTRATE FIRST EVIDENCE OF CLINICAL EFFICACY OF CANCER VACCINE IN PROSTATE CANCER Business Wire - Sept. 20, 2002

Dendreon Corporation announced the promising results of its first Phase III trial of Provenge(TM) (APC 8015), the company's investigational vaccine for the treatment of hormone resistant prostate cancer. Eric J. Small, M.D., professor of medicine and urology at the University of California San Francisco

and the trial's principal investigator, provided the first scientific presentation of the latest data on Provenge, which to date has been studied in trials enrolling more than 400 patients. Provenge is based on a new biologic approach that uses the body's own immune system to treat men suffering from the most advanced form of prostate cancer. The results showed that men with hormone resistant prostate cancer who have a Gleason score of 7 or less, which accounts for approximately 75 percent of hormone resistant patients, significantly benefited from Provenge treatment.

PROGENICS AND CYTOGEN REPORT POSITIVE PRECLINICAL RESULTS FOR EXPERIMENTAL PROSTATE CANCER DRUG-IN LABORATORY STUDIES, HUMAN MONOCLONAL ANTIBODY KILLED PROSTATE CANCER CELLS WHILE LEAVING NORMAL CELLS UNHARMED Business Wire - Sept 23, 2002

The PSMA Development Company announced encouraging preclinical results with its prostate cancer immunotherapeutic agent. The experimental drug is a human monoclonal antibody that targets prostate-specific membrane antigen (PSMA), a biological marker abundantly found on the surface of prostate cancer cells. In new laboratory studies, the monoclonal antibody killed PSMA-expressing cells, while sparing normal cells. "This monoclonal antibody has demonstrated an impressive ability to selectively deliver a lethal payload to PSMA expressing tumor cells," said William C. Olson, Ph.D., Progenics' vice president of research and development. "Our next steps include selecting the optimal toxin and radioactive payloads in parallel with producing clinical-grade antibody." "PSMA targeted therapies hold great promise for the treatment of prostate cancer, especially for patients in the advanced stages of the disease," said H. Joseph Reiser, Ph.D., president and CEO of CytoGen Corporation. "These early results indicate that the PSMA antibody has the potential to destroy prostate cancer cells without affecting normal cells in the body." PSMA is also present at high levels on the newly formed blood vessels (neovasculature) needed for the growth and survival of many types of solid tumors. If PSMA-targeted therapies can destroy or prevent formation of these new blood vessels, the therapies may prove valuable in treating a broad range of cancers. In addition to fully human monoclonal antibodies, the PSMA Development

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Company expects to initiate clinical studies of a therapeutic prostate cancer vaccine, pending acceptance of an investigational new drug (IND) application by the Food and Drug Administration (FDA). The vaccine is comprised of a recombinant PSMA protein and an immune stimulant or adjuvant.

CELSION PRESENTS HEAT ACTIVATED LIPOSOMES

Business Wire - Sept 20, 2002

Celsion Corporation presented a poster detailing Celsion's "New drug delivery approach for the treatment of prostate cancer". Dr. Donald "Skip" Trump reported on the anticipated start of human clinical trials of Celsion's investigational therapy for the treatment of prostate cancer. Celsion's therapeutic approach combines its proprietary focused-heat thermotherapy delivery system, the Microfocus BPH 800 Microwave Urethroplasty(TM) system, with a heat-sensitive liposome that is designed, when activated, to deliver a chemotherapeutic agent to the targeted tumor site. The Company will undertake Phase I clinical trials at Roswell Park. The technology employs specially designed liposomes, which open when heated. When the anticancer drug encapsulated in these liposomes is injected into the bloodstream of a cancer patient and the cancer treatment site is subjected to mild heat, the liposomes open and rapidly release their "load" of chemotherapeutic drugs directly at the treatment site. This release is significantly more rapid than in conventional liposomal therapy.

NEWS YOU CAN USE

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for screening resulted in the more frequent detection of small, organ-confined tumors without overdetecting possibly clinically insignificant ones

EVOLUTION OF THE PRESENTATION AND PATHOLOGIC AND BIOCHEMICAL OUTCOMES AFTER RADICAL PROSTATECTOMY FOR PATIENTS WITH CLINICALLY LOCALIZED PCA DIAGNOSED DURING THE PSA ERA

UROLOGY - Volume 60 Issue 3 (September 2002) Pages 458-463

With the introduction of serum PSA as a screening tool, we have noted an evolution toward a lower pathologic stage, grade, and improved PSA outcome. These findings provide further support that serum PSA screening increases the proportion of patients potentially curable

after radical prostatectomy

SIMPLIFIED MANAGEMENT OF POST-PROSTATE BIOPSY RECTAL BLEEDING

UROLOGY - Volume 60 Issue 3 (September 2002) Pages 508

Transrectal ultrasound-guided biopsy of the prostate is a common urologic procedure associated with low morbidity and mortality. On occasion, rectal bleeding occurs and can be effectively managed by temporarily inserting a tampon into the rectum.

STUDY EXPANDS LOOK AT HIGH-DOSE VITAMIN D WITH DOCETAXEL FOR PATIENTS WITH ADVANCED DISEASE

Researchers at Oregon Health and Science University have announced the launch of a national study to investigate the effect of high-dose vitamin D in combination with the chemotherapy agent docetaxel (Taxotere), for patients with advanced prostate cancer. The ASCENT (AIPC Study of Calcitriol Enhancing Taxotere) study is a multicenter, randomized, double-blind trial based on the promising results of a preliminary study in Oregon. ASCENT will determine whether a high dose of an active form of vitamin D, called calcitriol, taken once a week in combination with docetaxel, is any more effective than docetaxel alone for patients with androgen-independent prostate cancer (AIPC), an advanced form of prostate cancer.

ED UPDATE

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variety of reactions, ranging from subcutaneous nodules, intracavernosal fibrotic areas, and penile plaques, have been reported. The occurrence of fibrotic reactions with the use of papaverine alone or papaverine/phentolamine combinations has ranged from 0.5% to 31% and appears to be correlated with the number of injections and duration of therapy. In addition to instructing patients to alternate the side and site of injection, there is a growing body of evidence that suggests that PGE1 causes less fibrosis. It is postulated that fibrosis is caused by production of key cytokines, with transforming growth factor beta 1 (TGFB1) being the most important. Of significance, recent studies have demonstrated that PGE1 suppresses the production of TGFB1, reducing the amount of fibrosis. Notwithstanding, patients on trimix combinations need proper instruction on the penile injection technique and routine clinical follow-up to identify new onset of fibrosis. In most cases, penile nodules that occur with injection therapy disappear within a few months of stopping.

MEN NEED CHECKUPS

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a doctor when an autopsy is being performed on them to determine the cause of their death.

Does it make a man a real man when his kids don't have a father because he didn't go to the doctor and try to prevent an illness from spreading or becoming worse? Does it make a real man when his mother doesn't have a son anymore? Men should put their ego to the side and concentrate on their health first.

"Men aren't very educated health consumers," says Ken Goldberg, M.D., a urologist in Dallas, Texas, and founder of the Male Health Center. "They don't know much about their bodies, they're too embarrassed to say so, and when they have a problem, they don't know where to turn for help."

My theory is that this is one of the main reasons why legislatures can't solve most health care issues in our country. Men who are in power and make the final decision about health care don't go to the doctor themselves, so why would they be interested in proposing health care that's beneficial for other individuals?

According to Philadelphia's Jefferson Health System, there is a schedule of regular preventive checkups that men can do on a regular basis. Men in their 20s should have two checkups before they reach 30. Men in their 30s should have a checkup every three years.

Men in their 40s should have a checkup that includes early detection of prostate cancer, a DRE (digital rectal examination) every other year.

Men, age 50 and over, should have a checkup that includes DRE and PSA (prostate specific antigen) every year.

(Editors Note: Us Too! INTERNATIONAL recommends PSA and DRE beginning at 45 - at a minimum establishing a "baseline PSA" value. Men at higher risk should begin annual testing by 40 years of age.)

If men want to live a long life and enjoy their family, friends, grandchildren and retirement money, they should go to the doctor and receive regular checkups.

All men of any race, including myself, must take a moment and ask ourselves do we want our family and friends to one day say, "If he had gone to the doctor and had a physical and kept up with regular checkups he might still be around?"