STATE OF THE SCIENCE REPORT

Highlights From the 15th Annual PCF Scientific Retreat

October 2008

Provided with the compliments of the Prostate Cancer Foundation

pcf.org
# Table of Contents

Introduction 3

Key Areas of Discovery and Development 5

1. Nutrition, Metabolism and Bone Health 5

2. Inhibition of Androgen Activity 11

3. Implications for the Future of Genomics 14

4. Immunotherapy 16

5. Progression Biomarkers 20

6. Nanotherapeutics 26

7. Circulating Prostate Tumors Cells and MEMS 30

2008 Program Agenda 32
Introduction

The Prostate Cancer Foundation’s Annual Scientific Retreat brings together the world’s top physicians and scientists in a collaborative forum to share new data that might accelerate the end of death and suffering from prostate cancer. It is the most sought-after invitation in the world for prostate cancer scientists. This document has been prepared to share some of the “first reports” of research progress in prostate cancer from our 15th Annual Retreat, held this October on the shores of Lake Tahoe.

At this year’s retreat:

• 293 professionals attended the event including 115 M.D.s, 79 Ph.D.s, and 45 M.D., PhD.s.; many of the world’s most accomplished prostate cancer researchers participated;
• More than 20 Young Investigators presented data;
• Seventy-eight presentations ranging from basic science, to up-to-the-minute clinical results on new treatments for advanced prostate cancer were reviewed;
• 151 cancer research and treatment centers from 7 countries were represented;
• Two-and-a-half days of interaction with 28 hours of presentations and discussion provided a robust and thought-provoking agenda.

During the dinner programs, we celebrated our 19 PCF Young Investigators and the donors that made this $4.25 million program possible. Also at dinner, 11 multi-year team research grants—The PCF Challenge Awards—were highlighted. These programs were funded in the past few months.
The retreat program provided a forum for attendees to meet and network with our recently awarded PCF Young Investigators and to receive updates from our Challenge Awards Program teams. Also this year, there were an unprecedented number of lectures from “first time” attendees fulfilling the PCF mission of constantly attracting new human capital into the field.

We are pleased to report that our global community of researchers is indeed making crucial progress in further understanding this disease and developing new approaches to alleviate death and suffering from prostate cancer.

In his keynote address, PCF founder and chairman, Michael Milken, concluded that in spite of the current turbulence in our global financial markets, we are experiencing a golden age of progress in medical science. Having heard the ideas and progress made by PCF-supported investigators, we agree.

This report highlights seven key areas of progress that stood out from previous years. For those with a detailed interest, the agenda, listing every presentation from the retreat, is also provided. The highlights are intended to inform you of what’s new from the field and where research barriers remain. We hope that you will find this report enlightening. If you have specific questions, please contact us at dzenka@pcf.org.

Sincerely,

Jonathan W. Simons, M.D.    Howard R. Soule, Ph.D.
President & CEO     Executive Vice President
David H. Koch Chair & Chief Science Officer
1. Nutrition, Metabolism and Bone Health for Men with PCA

Presentation: *Prevention of Treatment-Related Fractures*

Investigator: Matthew Smith, M.D., Ph.D., Director of Research, Genitourinary Oncology Unit

Institution: Massachusetts General Hospital

PCF Funding: 5 Research Awards, 1998 - 2005

Key Findings:

- Androgen deprivation therapy (ADT) increases osteoporosis and bone fracture risk in prostate cancer survivors by reducing bone mineral density.
- Every patient should receive a baseline assessment of bone density and periodic checkups for bone density.
- Fractures can be prevented by several medications designed to increase bone mineral density during ADT.
  - Toremifene, an estrogen modulating medication, increases bone mineral density and decreases incidence of new vertebral fractures, reduces weight gain and decreases muscle loss.
  - Denosumab, a novel bone targeted therapy, increases bone mineral density and decreases incidence of new vertebral fractures. Ongoing clinical trials will evaluate Denosumab for prevention of bone metastases.

Discussion:

Dr. Matthew Smith reviewed updated clinical data on three drugs (Zometa, Denosumab and Toremifene) used to strengthen bone and prevent fractures in men treated with androgen deprivation therapy.
Zometa, which has already been marketed for several years, reduces bone fractures in patients treated with androgen deprivation therapy. These studies were led by Dr. Smith. The findings changed clinical practice and Zometa is currently the “drug of choice” for many patients with signs of osteoporosis while undergoing androgen deprivation therapy.

Two new agents, Denosumab from Amgen, and Toremifene from GTx are now in clinical trials under the leadership of Dr. Smith. Denosumab has completed pivotal clinical trials and is awaiting FDA approval. This medication stimulates bone growth in men at risk for fractures. Denosumab may provide a new treatment option for certain patients undergoing androgen deprivation therapy.

Toremifene, an orally active medication that modulates estrogen in men treated with androgen deprivation therapy is being developed with the leadership of Dr. Smith. Toremifene helps build bone mineral density, reduces fat, increases lean muscle mass and reduces fractures.

Dr. Smith’s update builds on a decade of PCF funding in bone biology and prostate cancer.

**Implications for Patients:**

By mitigating the negative side effect of loss of bone mineral density (BMD) associated with androgen deprivation therapy, these medications can enhance the quality of treatment and life for prostate cancer patients. Every patient on ADT should discuss their bone mineral density status and bone health with their oncologist.
Data shows that the incidence of bone fractures in patients undergoing androgen deprivation therapy increases measurably.

In clinical trials, patients taking Toremifene responded favorably with a lowered incidence of bone fractures compared to the patients taking the placebo.
Denosumab Increases BMD in Women Receiving Aromatase Inhibitor Therapy for Breast Cancer

In clinical trials Denosumab was demonstrated to increase bone mineral density in women receiving hormone therapy for breast cancer. This new agent may provide a treatment option for certain prostate cancer patients undergoing androgen deprivation therapy.

Presentation:  
*Update on Clinical and Basic Studies of Pomegranate Juice in Prostate Cancer*

Investigator:  
Dr. Alan Pantuck, M.D., Associate Professor of Urology

Institution:  
UCLA

Key Findings:

- Dr. Pantuck reported on 200 patients taking pomegranate juice as an antiprogression agent and antioxidant; all had recurrent prostate cancer.

- 35% of patients in the study who took 8 ounces daily of pomegranate juice achieved decreased PSA (range 5%–85%).

- 82.5% had prolonged PSA doubling time, a factor associated with improved survival.

- PSA doubling time appears to be durable.

- In laboratory studies pomegranate juice decreased cancer growth.
• POMx, a calibrated extract of pomegranate juice that has at least five times the antioxidant activity (potency) compared to 8 ounces of pomegranate juice, is entering clinical investigation for advanced prostate cancer.

• No significant side effects, including the onset of diabetes while taking pomegranate juice, were reported.

**Discussion:**

Dr. Alan Pantuck, professor of urology at UCLA has focused on nutrition and natural product treatment of recurrent prostate cancer. During the past five years, he has conducted several investigations of nutritional antioxidants. At this meeting Dr. Pantuck reviewed clinical trials data on the benefits of polyphenol antioxidants contained in pomegranate juice. Acting like a chemical sponge, antioxidants absorb reactive oxygen that is involved in the mutation of cancer cell DNA and the growth of tumor blood vessels. His findings showed that consuming 6-8 fluid ounces per day of pomegranate juice significantly slowed PSA doubling times, a common indicator of tumor progression, in patients with recurrent prostate cancer.

In experiments conducted by Dr. Alan Pantuck, pomegranate juice concentrate was shown to reduce both tumor weight and PSA levels in patients.

**Implications for Patients:**

This study highlights that interventional nutrition using a class of antioxidant plays an important role in prostate cancer prevention and treatment. Pomegranate juice (6-8 ounces per day) can slow the rate of rising PSA in many men with recurrent prostate cancer.
A concern with pomegranate juice was its high carbohydrate content. POM-X capsules, containing an extract of pomegranate juice, permits consumption of active ingredients of the juice without increasing carbohydrates in patients’ diets.

Ongoing clinical investigations are using POM-X pills that contain a calibrated extract of pomegranate juice. These pills do not contain sugars and possess at least five times the antioxidant potential of 6-8 ounces of pomegranate juice.
2. Inhibition of Androgen Activity

Presentation: ANDROGEN RECEPTOR Directed Therapy in Castration Resistant Disease: A Relevant Target or Misleading Decoy?

Investigator: Dr. Howard Scher, M.D., Chief of Genitourinary Oncology Service

Institution: Memorial Sloan-Kettering Cancer Center

PCF Funding: 12 Research Awards, 1994 – 2006; Charter Member of the Therapeutic Clinical Investigation Consortium

Key Findings:

- Clinical insights suggest that the androgen receptor still functions in many prostate cancer patients whose cancer appears to be resistant to Leupron or other medical hormonal therapy.

- Rising PSA levels on some patients are consistent with continued androgen receptor signaling.

- Identifying which patients have “under suppressed” androgen signaling, and who could respond to further targeted drugs versus true resistance, is an area of active research.

- Prostate cancer patients also respond to three new classes of hormone therapies including Abiraterone, Medivation-3100 and BMS-6411988.

- These three new classes of anti-androgen receptor inhibiting agents are all in clinical trials at the eight clinical centers that comprise the PCF-Department of Defense Clinical Therapy Consortium.

Discussion:

Dr. Howard Scher convened a session on the androgen receptor. The results of several drugs in development targeting androgen activity and androgen reception in prostate cancer were discussed. Experimental medications included Abiraterone (Cougar Biotechnology), MDV3100 (Medivation), and BMS-641988 (Bristol-Myers Squibb). Abiraterone is currently in Phase III clinical trials for prostate cancer in patients following conventional androgen deprivation and chemotherapy. MDV3100 and BMS-641988 are approaching Phase II clinical trials. All three of these therapeutics are new classes of agents compared with existing drugs.
While standard androgen deprivation therapy produces clinical remissions in most prostate cancer patients, the majority of patients will become resistant to this therapy eventually. Androgen (testosterone) synthesis in some tumor cells continues to fuel tumor growth even with treatment with Leupron. This is exactly where Abiraterone acts. Dr. Scher presented encouraging data that Abiraterone can cause tumor regression in patients who failed standard hormonal therapy.

MDV3100 and BMS641988 inhibit the androgen receptor directly in ways very different from current medications in this class. Dr. Scher shared data from collaborators that these medications block the translocation of the androgen receptor inside the nucleus where it causes prostate cancer cells to grow and survive. Early clinical data was shown for these two agents. PSA levels are clearly reduced in a large proportion of treated patients. Side effects, as reported at the PCF retreat, appear to be modest and manageable in outpatients. Phase II trials are scheduled to begin in early 2009 and will define the BEST dose and clinical benefit of these encouraging agents. The complexity of signaling for the androgen receptor is depicted below in a slide provided by Dr. Scher.

The Alterations in AR Identified in CRPC Represent Potential Targets for Therapy(ies)

While androgen signaling is indeed complex, Dr. Scher highlighted specific targets that can be affected by Abiraterone, MDV-3100 and BMS-641988.

It’s important to note that the PCF funded a great deal of the science that supported the discovery and development of these medications to block pathways that need to be shut off in order to induce a remission. In the area of androgen receptor and hormone biology in prostate cancer, the PCF continues to fund new developments through a Challenge Award to Dr. Peter Nelson at the University of Washington and Dr. Stephen Balk with Beth Israel Deaconess Hospital/Harvard Medical School in Boston. This award will
further define the mechanism of action of Abiraterone and the reason(s) for inevitable resistance. Another Challenge Award to Dr. Scher and collaborators at Memorial Sloan-Kettering Cancer Center focuses on discovering progression biomarkers that will speed the development of new androgen antagonizing medications. The PCF continues to invest in this vital area of research with near-term patient benefits.

**Implications for Patients:**

Many patients may be able to achieve another remission following progression of the disease. The exact percentage will not be known until studies with hundreds of patients are completed. These studies are underway. If the Phase III clinical investigation of Abiraterone is successful, patients who fail standard hormonal therapy will have a new, effective treatment strategy within the next four to five years. Patients can benefit sooner from Abiraterone or the two other medications, MD-3100 and BMS-641988, discussed above by participating in clinical trials. Research in this area will also define which patients have resistant disease at the onset of hormonal therapy and need a different set of targeted agents.
3. Implications for the Future of Genomics

Presentation: Cancer Genome Research: Prospects for the Future
Investigator: Todd Golub, M.D., Director, Cancer Program
Institution: Broad Institute of Harvard and MIT
PCF Funding: 1 grant, 2008

Key Findings:

- Robotic, high-speed sequencing of the prostate cancer DNA genome from patient biopsies of metastases will reveal new targets and therapeutic strategies.

- The exact number of mutated genes that might be targets for new drugs is not known, but several candidates were presented.

- The work is exceptionally expensive, but is becoming less and less labor intensive with the speed of technology and use of robots.

- There is an urgency for this information to translate to new patient treatments and a shortage of metastatic biopsies for researchers.

- Most new prostate cancer targets discovered by this new biotechnology may be difficult to inhibit with 20th century chemical strategies used by pharmaceutical companies.

- Much of the genome remains functionally undefined and most of the prostate cancer genes have yet to be studied.

Discussion:

Complete sequencing of the three billion genetic letters in the genome of a cancer patient will soon be a practical reality. But the forward-looking presentation of Dr. Golub focused on the delivery of this massive amount of complex information to patients, and how low-cost diagnostic tests that match patients to therapies will have an impact on patient treatment. These tests will optimize treatment for a genetic lesion for which a medication has been shown to be effective instead of treating prostate cancer, breast cancer, lung cancer, etc. Obtaining a complete genome characterization of each patient is a goal for knowledge-based therapy.

Genomic research with DNA sequencing is yielding many new targets and treatment strategies for prostate cancer. These are being posted for the biotechnology and pharmaceutical industries and university researchers in several publicly accessible databases including the PCF. These new targets are likely to be difficult to inhibit with...
conventional pharmaceutical methods developed in the 20th century to create chemotherapeutic drugs. It is likely the new classes of drugs to block target genes will require different chemistry and drug delivery chemistries. Dr. Golub calls this process “drugging the currently undruggable” targets. The PCF recognizes this complexity which is the basis of Dr. Golub’s Challenge Award. The goal of his research is to identify inhibitors of downstream cancer-causing genetic changes in prostate cancer. These targets are likely to be genetic regulatory factors and will require the discovery of very creative pharmaceutical solutions. The team at the Broad Institute, MIT and Harvard University, (all participants in the PCF Challenge Award) has been funded as part of a worldwide competition to attack and solve these complex issues in creating new targeted drugs for prostate cancer.

**Implications for Patients:**

Although these efforts are still in their pioneering stage, the concept of being able to treat cancer by specifically treating the mutated genes that caused it has validation in chronic myelogenous leukemia, HER2 over-expressing breast cancers, and some lung cancers. Human prostate cancer needs its own list of critical targets in addition to the androgen receptor.
4. Immunotherapy

Presentation:  
**Checkpoint Blockade in Prostate Cancer: New Opportunities**

Investigator:  James Allison, Ph.D., Program Chairman of Immunology

Institute:  Memorial Sloan-Kettering Cancer Center

PCF Funding:  7 grants, 1997 - 2006

Conclusions:

- >3700 patients (most melanoma) have been treated with Ipilimumab.
- Approximately 200 prostate cancer patients have been treated with this medication so far.
- Approximately 10% of prostate cancer patients exhibit declines in PSA when treated with Ipilimumab. Why a majority of patients do not respond is now an area of intense research.
- A potential blood test of immune cell function called ICOS may define which patients will have remission with treatment.
- Clinical remissions have been recorded in melanoma, renal, prostate, ovarian and Hodgkins-related cancers.
- There is an ~15% response rate in melanoma as monotherapy, including durable complete responses.
- Rate of response seems to be higher when combined with other immunizing strategies.

Discussion:

Dr. Allison discovered the first checkpoint of the human immune response which is designated CTLA-4. Ipilimumab is a monoclonal antibody that blocks CTLA-4 and essentially “takes the brakes off” of the immune response. The drug is powerful. While it has been effective in approximately 15% of treated patients, the side effects of autoimmune reactions can be complex and require hospitalization. Having “brakes” on the immune response is an important component of normal health, as it prevents the immune system from attacking and destroying normal healthy tissue. Prostate cancer, however, has several ways it activates this checkpoint as a means of evading detection and eradication by the immune system.
Ipilimumab releases the immune system’s brakes, enabling mild vaccines and the patient’s own tumor to attack the cancer. The goal of such therapy is to use the eradicating power of the patient’s immune system to destroy prostate cancer. The PCF’s Challenge Award that went to Pam Sharma at M.D. Anderson Cancer Center and Jim Allison, PhD at Memorial Sloan-Kettering Cancer Center will focus on the discovery of molecules that will predict which patients will respond to Ipilimumab while identifying patients who may be at advanced risk of an adverse effect from Ipilimumab. Much more work in this area is needed to dissect why individual patients and their immune activation varies. It’s an entirely new avenue of research for a form of treatment. An implication from this work, as presented this year in Tahoe, is that oncologists will need to learn to manage some patients through the side effects of Ipilimumab in order to steer patients into remissions. While preliminary, data in some melanoma and prostate cancer patients suggest that if a remission is generated, it may be very long lasting without repetitive treatment. This suggests the immune system has been reset to keep attacking and killing cancer cells without additional antibody treatment.

Liver scans depict favorable patient response to treatment with Ipilimumab. The new lesions detected in Week 12 are not visible in Week 36.

While FDA approval of Ipilimumab is potentially four to six years away, patients can benefit sooner by speaking to their physicians about participating in an Ipilimumab clinical trial.
**Presentation:**  Additional Immune Checkpoints in Prostate Cancer: PD-1 and LAG-3

**Investigator:** Charles Drake, M.D., Ph.D., Assistant Professor, Medical Oncology, Immunology and Urology

**Institution:** Johns Hopkins Medical Institutions

**Key Findings:**

- Prostate cancer is infiltrated with specific T cells that are biologically blocked from killing tumors by a newly discovered resistance molecule named PD-1. It is a brake or checkpoint of the immune system that prevents the immune system from attacking tumor cells.

- Phase I Trial of PD-1 blocking antibody is completed.

- The blocking antibody was relatively well-tolerated and evidence of immune activity was demonstrated.

- Checkpoint blockade with vaccination will be studies in future investigations.

- LAG-3 is another immune checkpoint that is being studied for its role in hiding prostate cancer cells from the immune system.

**Discussion:**

Dr. Charles Drake from Johns Hopkins presented new information on immune checkpoints that may present additional therapeutic opportunities. Directing the immune system to eradicate prostate cancer from patients may require more than one approach. Drs. Allison and Drake discussed basic science findings suggesting several checkpoints that can be therapeutically blocked in prostate cancer patients to allow the immune system to attack metastatic prostate cancer cells. These checkpoint genes include PD-1, LAG-3, and others in the B7-X family.

Dr. Drake reviewed data from a Phase I trial he has concluded for PD-1 checkpoint inhibition using a monoclonal antibody. He observed clinical responses without serious side effects. Side effect profiles will also be fully investigated by dose escalation. We will be carefully tracking the results of immunotherapy clinical trials and emerging checkpoint biology research in the coming months.
In clinical trials with melanoma patients, a PD-1 blocking antibody was shown to result in reduced tumor size at 12 weeks following the first dose and at 3 weeks following a third dose. The presence of the antibody in the cancer cells can be seen in red.
5. Progression Biomarkers

Presentation:  *Circulating MicroRNAs as Stable Blood-Based Markers for Cancer*

Investigator:  Muneesh Tewari, M.D, Ph.D., Assistant Member, Human Biology

Institution:  The Fred Hutchinson Cancer Center

Key Findings:

- An entirely new class of fragments from cancer cells may be detected in the blood, and may be more specific for cancer activity than the PSA test.

- This new class of molecules are small strips of ribonucleic acid RNA.

- Small regulatory RNA molecules, termed miRNA, are stable in blood which usually degrades RNA in larger forms, making this a scientific surprise.

- miRNAs are involved in the malignant cells growth and survival so their presence in the blood signals cancer activity.

- Laboratory models proved that prostate cancer-derived miRNAs can be detected in blood.

- Levels of one miRNA, designated miR-141, identify patients with prostate cancer.

Discussion:

Dr. Muneesh Tewari from Fred Hutchinson Cancer Center at University of Washington discovered MIR-141 is a cancer-associated micro-RNA. He shared research results on the characterization of this micro-RNA and the development of a miR-141 based diagnostic test to identify prostate cancer with a simple blood test. Tewari was studying MIR-141 and others when he asked the simple question: could it be detected in the blood of patients if it was working with their tumor cells? Most scientists would have scoffed at wasting time even testing this idea as most RNA molecules are degraded in the human blood almost instantaneously by enzymes that are in the serum. Tewari, however, was aware that micro-RNAs showed unusually high stability in tissue specimens and on a hunch decided to test whether this stability extended to blood as well.
miR-141 is a cancer-associated micro-RNA that exhibits moderate to high expression in human prostate cancer tissue. Surprisingly, it does not degrade in blood serum, providing a new, more precise tool for assessing prostate cancer growth or regression after a given treatment.

The PCF-funded group in Seattle, Drs. Peter Nelson and Robert Vessella have been assisting Dr. Tewari as collaborators with prostate cancer expertise. Dr. Tewari, who was not a prostate cancer expert eight months ago, is now collaborating daily with some of the world’s leading scientists whose laboratories are in immediate proximity. An important principle for biomarkers is that although PSA is prostate specific, it’s not cancer specific. Both normal and malignant prostate cells produce PSA, causing PSA levels to change for a host of reasons that are not necessarily related to cancer progression.

New biomarkers, including miR-141, may prove to be more prostate cancer specific in the blood, and are not changed by hormone treatment. This may allow more precise assessment of prostate cancer growth or regression after a given treatment. Dr. Tewari has developed a blood test to measure miR-141 in human blood samples. His work might also be applicable to patients with other solid tumors especially ovarian cancer.

Dr. Tewari reported that his technology for detecting micro-RNAs as “diamond dust” in the blood that only is found with tumor activity is one that the Fred Hutchinson Cancer Research Center is actively seeking industrial partners for in order to develop the findings into a clinically useful diagnostic procedure. The PCF will be monitoring the development of the biotechnology and offering to provide access to biobanks of specimens to accelerate validation of a new a clinical test.
Presentation: PCA-3 and Gene Fusion Based Diagnostics of Prostate Cancer

Investigator: Jack Schalken, Ph.D., Research Director of Urology

Institution: Nijmegen Center for Molecular Life Sciences

Key Findings:

- PCA-3 is the first DNA diagnostic test for prostate cancer to be discovered in comparing prostate tumor DNAs to normal DNAs.
- PCA-3 is being rigorously tested in multiple clinical settings in Europe and the U.S. for the diagnosis of prostate cancer.
- PCA-3 biomarker may have a significant impact on the diagnosis and staging of prostate cancer using it in urine testing.
- A second molecular test under development is the detection of a gene fusions thought to drive prostate cancer (TMPRSS2-ERG).

Discussion:

Jack Schalken, Ph.D. from the University of Nijmegen in the Netherlands presented an update on two important molecular diagnostic tests for prostate cancer. One detects the presence of PCA-3, a prostate cancer-associated gene, and the other tests for the presence of the TMPRSS2-ERG (T2-Erg) gene fusion. Both of these tests can be performed on cells found in the urine. Both are found only in cancer cell DNA, so both are specific for cancer cells, unlike PSA.
What is measured in the urine post-DRE?

The higher the PCA3 Score, the greater the likelihood of a positive repeat biopsy.

Following a digital rectal exam (DRE), a simple urine sample can collect both regular and cancerous prostate cancer cells. As the PCA3 level found in the prostate cancer cells rises, so does the risk of a positive repeat biopsy.
Currently, the PCA-3 test is approved for diagnostic use in Europe and is widely available at reference labs in the U.S. Schalken’s findings suggest that this test may be superior to PSA with respect to identifying patients that may need aggressive therapy. Research on T2-ERG detection in urine is at an earlier stage of development. The assays are not mutually exclusive. Dr. Schalken noted that information on diagnosis and prognosis will likely increase by combining reports from these molecular tests as a battery of tests.

**Presentation:** *Nuclear-Structure Based Serum Markers of Prostate Cancer*

**Investigator:** Robert Getzenberg, Ph.D., Professor, Urology, Pharmacology and Molecular Science

**Institution:** Johns Hopkins University

**PCF Funding:** 2 Research Awards, 2005 - 2006

**Key Findings:**

- Unlike micro RNAs, or DNA tests like gene fusions, EPCA-2 is a prostate-cancer-specific biomarker protein.

- Antibodies have been produced to develop a lab test to detect EPCA-2 being release from early prostate cancer.

- Applications include (1) risk stratification for prostate cancer detection and (2) identifying individuals with elevated PSA levels and/or positive DREs that will have a high probability of a positive biopsy of the prostate.

- EPCA2 for distinguishing individuals with organ-confined disease from those with more aggressive disease (local vs. distant disease).

- EPCA-2 might be useful as a biomarker of disease progression and for measuring therapeutic response.

**Discussion:**

Dr. Robert Getzenberg from John Hopkins discussed a test for the EPCA-2, cancer-specific protein molecule. He presented results related to the characterization of an EPCA-2 test in post-prostatectomy patients, and showed that patients with potentially curative surgery revert to a zero EPCA-2 value.

Studies evaluating EPCA-2 as a marker for disease recurrence and as a biomarker to inform treatment efficacy are ongoing. We are hopeful that John Hopkins will be
successful in developing EPCA-2 into a robust progression biomarker and in licensing its EPCA-2 technology in the near future for development of a commercial clinical lab test. We also hope this test will be available to patients within two years of Hopkins obtaining a commercial partner.

Assessing EPCA-2 biomarkers found in blood and urine effectively differentiates patients with prostate cancer from those with prostatitis and can be used to verify patient response to treatments.

Implications for Patients:
Better diagnosis and enhanced tools for tracking disease progression should save countless lives. Several diagnostic tests that should improve upon PSA testing and detect cancer earlier are progressing through the development process. The potential for advanced biomarkers to measure patient response to treatments is another important application that can speed development of new medications and provide a more accurate patient prognosis. Unlike four years ago, there are now candidate biomarkers from protein (EPCA-2), DNA (PCA-3 and Gene Fusions), and RNA (mi141) – all materials that appear to be uniquely produced by tumor cells and detectable in blood or urine.
6. Nanotherapeutics

**Presentation:**  *Safeway-PCF STAR in Temperature Enhanced Metastatic Therapy*

**Investigator:**  Robert Getzenberg, Ph.D., Professor, Urology, Pharmacology and Molecular Science

**Institution:**  Johns Hopkins University

**PCF Funding:**  2 Research Awards, 2005 - 2006

**Key Findings:**

- Characteristic changes occur in tumors when temperature is increased to about 105 degrees F; these might enhance anti-tumor agents killing.

- Heat induced changes include CIRBP, RBM3, and RNA binding, and “cold shock” of proteins and genes that might mediate reduced tumor cell survival with heat.

- Alteration of CIRBP and RBM3 levels appear to synergize the effects of radiation therapy and chemotherapeutic agents and increase the number of tumor cells killed/dose.

**Discussion:**

This collaborative research program is led by Dr. Getzenberg of Johns Hopkins and investigators at the University of Michigan and the University of British Columbia. The program is called TEMT for temperature-enhanced metastatic therapy. The concept is that tumor cells cannot handle the stress of heating to about 105 degrees F compared to normal cells and they die at this temperature when treated with anticancer drugs unlike normal cells. Delivering targeted heat is the critical challenge in bioengineering. Dr. Getzenberg described this program that uses iron nanoparticles specifically targeted for uptake by prostate cancer cells. These particles will be injected into patients with advanced metastatic prostate cancer, where they will concentrate at sites where the cancer has metastasized. An oscillating magnetic field will be applied causing an increase in temperature in the cancer cells. Increasing the temperature of prostate cancer cells can activate many normal cell-killing mechanisms that will enhance the effect of standard chemotherapy. Promising preliminary data were presented by Dr. Getzenberg and full proof of principle is expected by the end of 2008.
Nanoparticles Targeted for Prostate Cancer

When injected into patients, targeted nanoparticles home in on the membranes of prostate cancer cells, where they are naturally ingested by the cell. When the temperature of prostate cancer cells is increased by an oscillating magnetic field, normal cell-killing mechanisms are activated that will enhance the effect of standard chemotherapy.

**Presentation:** Koch-PCF Nanomedicine Research Program

**Investigator:** Omid Farokhzad, M.D., Assistant Professor, Anesthesiology,

**Institution:** Brigham and Women’s Hospital

**Key Findings:**

- Prostate-cancer-targeted nanoparticles loaded with anti-tumor drugs like taxotere are a new treatment strategy. They can deliver far higher doses of drugs to tumor cells without compromising healthy cells.

- Encapsulation of chemotherapeutic drugs into biodegradable nanoparticles has been accomplished with new chemistry invented at MIT and Harvard.

- Targeted nanoparticles can be programmed to dock only on prostate cells and be taken up like Trojan horses.
Discussion:

Results of the Koch-PCF nanomedicine program were presented by Omid Farokhzad, M.D., of the Brigham and Women’s Hospital. This program is being conducted in collaboration with Dr. Robert Langer of MIT, Dr. Philip Kantoff of the Dana-Farber Cancer Institute, and Dr. Neil Bander of the Weill Cornell Medical College. In this project, polymer based nanoparticles have been bioengineered to target prostate cancer cells and to deliver antineoplastic payloads. Upon injection, these nanoparticles home to prostate cancer tumors in experimental models. These tumors are subsequently killed when the contents of the nanoparticles are spilled into the interior of the tumor cell. This “Trojan horse” approach to targeted therapy will minimize toxicity of anti-tumor drugs and expand the capability of delivering many classes of cancer medications. Normal cells do not permit entry of the nanoparticle because they only “dock” on the surface of prostate cancer cells with the Prostate Specific Membrane Antigen whose biology was research by Dr. Neil Bander at Cornell University in the 1990s. This is inherently different from standard chemotherapy in which the active compound is systemically distributed, exposing normal cells to toxic side effects.

![Image: Acting like Trojan horses in the body, targeted nanoparticles filled with cancer-killing payloads show potential for delivering therapeutic compounds directly into prostate cancer cells while avoiding healthy cells.](image-url)
Implications for Patients:

The first-in-man studies of prostate-cancer-targeted nanotherapeutics is expected within one year. If nanotherapeutics demonstrate that Trojan Horses can deliver entirely new agents into prostate cells, and entire new set of possible drugs could be used to treat prostate cancer that only lack a biotechnology that can “trick” a tumor cell into taking up the drug.
7. Circulating Prostate Tumor Cells and Micro Electronic Machines

Presentation: New Approaches to Detecting Circulating Tumor Cells
Investigator: Daniel Haber, M.D, Ph.D., Director
Institution: Massachusetts General Hospital Cancer Center
PCF Funding: 1 Research Award, 2008

Conclusions:

- Microfluidic MEMS (MicroElectronic Machines) is a breakthrough technology for circulating tumor cell (CTC) isolation and characterization.
- Presence of CTCs in numbers higher than suspected across multiple tumor types.
- In lung cancer, this test provides a noninvasive serial monitoring for response and molecular mechanisms of resistance.
- In prostate cancer, it has potential applications for analysis of “localized” disease and disease progression.

Discussion:

A novel microfluidic microelectromechanical systems (MEMS) device, developed by Drs. Daniel Haber and Mehmet Toner of Massachusetts General Hospital Cancer Center, enables a simple blood test to detect and characterize the circulating tumor cells (CTCs) responsible for metastasis. Although it is not yet approved for clinical use, it may eventually play a key role in numerous aspects of cancer diagnosis and treatment, including detecting and evaluating metastatic disease, selecting and individualizing initial surgical and medical therapies, monitoring disease progression, detecting the occurrence of therapy-induced mutations and the consequent development of resistance, and understanding the fundamental biology of metastasis.

Current detection methods successfully detect CTCs in only half of samples known to contain them. The new device consists of approximately 80,000 micro posts covered with antibodies against the epithelial cell adhesion molecule (EpCAM), permitting them to selectively bind CTCs. The bound cells are visualized with fluorescent staining and optical microscopy. The device has been used to detect CTCs from prostate, lung, breast and gastrointestinal cancers. Staining techniques for specific molecules, such as prostate specific antigen (PSA), provide reliable confirmation of the source of the CTC.

The PCF is funding the next phase of research being conducted with the MEMS device developed Drs. Haber and Toner. Using the device, Drs. Rick Lee and Matthew Smith at
the Massachusetts General Hospital Cancer Center are directing clinical trials to analyze CTCs in prostate cancer patients. The research seeks to validate prostate cancer applications for CTC analysis similar to those already shown for lung cancer. The clinical trials include correlating CTCs with borderline or rising PSA levels, pathological and histological analysis, and the likelihood of post-operative recurrence; rapidly measuring therapeutic responses; detecting the development of resistance and genetic changes, such as translocation and androgen receptor mutation; and understanding the disease process to identify diagnostic markers and novel therapeutic targets.

Once extremely difficult to capture, characterize and count, circulating tumor cells can now be captured on the micro-posts of a MEMS device as seen in the scanning electron image on the right. Tumor volumes exhibit a correlation to the number of CTCs found in blood samples as shown by the data from a lung cancer patient.

Implications for Patients:

This technology provides a minimally invasive technique for early detection of tumors and metastasis. A single cancer cell can be isolated from over a billion red blood cells in a routine blood test using this new convergence of microelectronics, material sciences, and molecular biology. We call this approach at the PCF a “Liquid Biopsy” for progression biomarkers. We have an enormous amount to learn about the strengths and limitations of these liquid biopsies and how to apply them to routine daily care of patients. Analysis of CTCs can indicate the type of cancer, its aggressiveness, and its susceptibility to particular treatments. New biotechnologies allow a single isolated tumor cell in a patient to be analyzed for genes that can help predict response to drugs before they are used. Also, it may be possible to measure remissions earlier using liquid biopsies that using conventional CT scans and other radiology tests. Although the absolute number of CTCs in the blood did not correlate to tumor size, variations in CTC levels over the course of treatment do correlate with X-Ray evaluations of progression and remission, providing an important and responsive means of monitoring the efficacy of standard or experimental regimens.
Welcome and Introduction

2:45PM – 3:00PM Prospection on Prostate Cancer Research Frontiers: 2008-2009
Jonathan Simons, MD
Prostate Cancer Foundation

Session I: Nutrition, Metabolism, and Bone Health

3:00PM – 5:30PM Moderator:
Matthew Smith, MD, PhD
Massachusetts General Hospital

3:00PM – 3:20PM Prevention of Treatment-Related Fractures
Matthew Smith, MD, PhD
Massachusetts General Hospital

3:20PM – 3:40PM Nutritional Modulation of Oxidant Stress, Immune Function, and Prostate Cancer
David Heber, MD, PhD
University of California, Los Angeles

3:40PM – 4:00PM The IGF System Integrates Genetic and Environmental Signals to Control Longevity and Health
Pinchas Cohen, MD
University of California, Los Angeles

4:00PM – 4:20PM Modulating Prostate Cancer Progression by Targeting the Akt/mTOR Pathway through Dietary Intervention
Linda deGraffenried, PhD
University of Texas Health Science Center at San Antonio

4:20PM – 4:40PM Discussion
Update on Supplements

4:40PM – 5:30PM

4:40PM – 5:00PM  Role of Herbal Anti-Inflammatory Compounds in Prostate Cancer Prevention
Aaron Katz, MD
Columbia University

5:00PM – 5:20PM  Update on Clinical and Basic Studies of Pomegranate Juice in Prostate Cancer
Alan Pantuck, MD
University of California, Los Angeles

5:20PM – 5:30PM  Discussion

Session II: Collision of Technology and Biology – Next Generation of Genetic Technology

5:30PM – 7:00PM  Moderator:
Philip Kantoff, MD
Dana-Farber Cancer Institute

5:30PM – 5:40PM  Introduction
Philip Kantoff, MD
Dana-Farber Cancer Institute

5:40PM – 6:00PM  “Next-Generation” Sequencing Technology for Cancer Genome Characterization
Levi Garraway, MD, PhD
Dana-Farber Cancer Institute

6:00PM – 6:20PM  Toward a Panoramic View of the Lethal Prostate Cancer Genome
John Carpten, PhD
Translational Genomics Research Institute

6:20PM – 6:40PM  Cancer Genome Research: Prospects for the Future
Todd Golub, MD
Broad Institute of Harvard and MIT

6:40PM – 7:00PM  Discussion

7:00PM – 10:00PM  Dinner and Poster Session

7:00 – 8:00PM  Dinner
7:45 – 8:00PM  Special Presentation: 2008 Challenge Award Recipients
Howard Soule, PhD
Prostate Cancer Foundation

8:00 – 10:00PM  Poster Session
Friday, October 17, 2008

Session III: Immunotherapy

7:30AM – 9:40AM

7:30AM – 8:30AM  PANEL DISCUSSION
The Yin and the Yang of Ipilimumab for Prostate Cancer and Melanoma

Moderator:  Eric Small, MD
University of California, San Francisco

Panelists:  Tomasz Beer, MD
Oregon Health & Science University
Susan Slovin, MD, PhD
Memorial Sloan-Kettering Cancer Center
Winald Gerritsen, MD, PhD
VUMC – Amsterdam
Omid Hamid, MD
The Angeles Clinic and Research Institute

8:30AM – 9:00AM  Panel Question & Answer Session

Immune Checkpoint Biology

9:00AM – 9:40AM

9:00AM – 9:15AM  Checkpoint Blockade in Prostate Cancer: New Opportunities
James Allison, PhD
Memorial Sloan-Kettering Cancer Center

9:15AM – 9:30AM  Additional Immune Checkpoints in Prostate Cancer: PD-1 and LAG-3
Charles Drake, MD, PhD
Johns Hopkins University

9:30AM – 9:40AM  Discussion

9:40AM – 10:10AM  SPECIAL LECTURE
Human Biospecimens: The Fuel for Translational Research and the Currency of Molecular Medicine
Carolyn Compton, MD, PhD
National Cancer Institute

Introduced by: Howard Soule, PhD – Prostate Cancer Foundation
Session IV: The Androgen Axis

10:10AM – 11:45AM  Moderator: Howard Scher, MD
Memorial Sloan-Kettering Cancer Center

10:10AM – 10:30AM  AR-Cell Cycle Crosstalk: Implications for Prostate Cancer Progression and Management
Karen Knudsen, PhD
Thomas Jefferson University

10:30AM – 10:50AM  Androgen-Dependent Mechanisms and Epigenetic Control of Prostate Cancer
Michael Rosenfeld, MD
University of California, San Diego

10:50AM – 11:10AM  Reprogrammed Androgen Receptor in Androgen-Independent Prostate Cancer
Myles Brown, MD
Dana-Farber Cancer Institute

11:10AM – 11:30AM  AR Directed Therapy in Castration Resistant Disease: A Relevant Target or Misleading Decoy
Howard Scher, MD
Memorial Sloan-Kettering Cancer Center

11:30AM – 11:45AM  Discussion

11:45AM – 11:55AM  SPECIAL PRESENTATION TO WINTER VINECKI
PCF Everyday Hero & WebMD 2008 Health Hero
Scott Zagarino
Athletes for a Cure
Introduced by: Dan Zenka – Prostate Cancer Foundation

12:00PM – 1:00PM  Keynote Address
Mike Milken
Prostate Cancer Foundation
Introduced by: Stuart Holden, MD - Prostate Cancer Foundation
Session V: ETS Gene Rearrangements – New Developments

2:30PM – 4:15PM  Moderator:
Mark Rubin, PhD
Weill Medical College of Cornell University

2:30PM – 3:00PM  Specificity within the ETS Family of Transcription Factors
Barbara Graves, PhD
University of Utah

3:00PM – 3:20PM  Using ETS Gene Fusions to Understand Prostate Cancer Biology
Scott Tomlins, PhD
University of Michigan

3:20PM – 3:40PM  ETS Rearrangement, Prostate Cancer, and Heterogeneity
Mark Rubin, MD
Weill Medical College of Cornell University

3:40PM – 4:00PM  TMPRSS2-ERG: The Other Half of the Story
Peter Nelson, MD
Fred Hutchinson Cancer Center

4:00PM – 4:15PM  Discussion

Session VI: Special Project Updates

4:15PM – 5:45PM  Moderator:
Donald Coffey, PhD
Johns Hopkins University

4:15PM – 4:30PM  The Evolution of Cancer and the Evolution of Therapy
Donald Coffey, PhD
Johns Hopkins University

4:30PM – 4:50PM  Safeway-PCF STAR in Temperature Enhanced Metastatic Therapy
Robert Getzenberg, PhD
Johns Hopkins University

4:50PM – 5:10PM  Koch-PCF Nanomedicine Research Program
Omid Farokhzad, MD
Brigham and Women’s Hospital

5:10PM – 5:30PM  PCF Bone Targeting Therapy Preclinical Models Consortium
Robert Vessella, PhD
University of Washington
5:30PM – 5:45PM  Discussion

6:00PM – 6:15PM  PCF-DoD Prostate Cancer Clinical Trials Consortium (PCCTC)
Prostate Cancer Patients Experiencing Treatment Sciences
Howard Scher, MD - Memorial Sloan-Kettering Cancer Center
Howard Soule, PhD - Prostate Cancer Foundation

6:15PM – 6:45PM  Translational Studies: A Methodologic Perspective
Steve Piantadosi, MD, PhD
Cedars-Sinai Medical Center

Introduced by: William Nelson, MD, PhD – Johns Hopkins University

6:45PM – 7:00PM  Discussion

7:00PM – 8:15PM  Dinner

7:30PM – 8:00PM  Special Presentation: Presentation of 2008 PCF Young Investigators
Donald Coffey, PhD
Johns Hopkins University

8:30PM – 10:00PM  INDECISION 2008 (WITH APOLOGIES TO JON STEWART)
Townhall Discussion: Amplification of Research to End Death and Suffering from Prostate Cancer
Donald Coffey, PhD - Johns Hopkins University;
Neal Rosen, MD, PhD – Memorial Sloan-Kettering Cancer Center
Saturday, October 18, 2008

8:15AM – 8:45AM The Epigenetics of Prostate Cancer: Finally Delivering New Tests and New TreatmentsS
William Nelson, MD, PhD
Johns Hopkins University

Introduced by: Jonathan Simons, MD - Prostate Cancer Foundation

Session VII: Principles of Targeted Therapy

8:45AM – 11:00AM Moderator:
Neal Rosen, MD, PhD
Memorial Sloan-Kettering Cancer Center

8:45AM – 9:15AM Feedback and Redundancy in Oncoprotein Signaling Pathways – Basic and Clinical Implications
Neal Rosen, MD, PhD
Memorial Sloan-Kettering Cancer Center

9:15AM – 9:35AM The Hedgehog Pathway in Cancer: The Discovery of IPI-926
Julian Adams, PhD
Infinity Pharmaceuticals, Inc

9:35AM – 9:55AM Appropriate Application of IGF-IR Inhibition in Prostate Cancer
Steve Plymate, MD
University of Washington

9:55AM – 10:25AM Identification of Cancer Co-Dependencies with Functional Genomics
William Hahn, MD, PhD
Dana-Farber Cancer Institute

10:25AM – 10:40AM PTHrP-induced Stabilization of Androgen Receptor Promotes Prostate Cancer Cell Growth
Michael Weber, PhD
University of Virginia

10:40AM – 11:00AM Discussion
Session VIII: Progression Biomarkers – The Quest for Sensitivity and Specificity

<table>
<thead>
<tr>
<th>Time</th>
<th>Session Title</th>
<th>Presenter</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>11:00AM – 11:20AM</td>
<td>New Approaches to Detection of Circulating Tumor Cells</td>
<td>Daniel Haber, MD, PhD</td>
<td>Massachusetts General Hospital</td>
</tr>
<tr>
<td>11:20AM – 11:40AM</td>
<td>Nuclear Structure-Based Serum Markers of Prostate Cancer (EPCA-2)</td>
<td>Robert Getzenberg, PhD</td>
<td>Johns Hopkins University</td>
</tr>
<tr>
<td>11:40AM – 11:55AM</td>
<td>Predictive Models in Prostate Cancer</td>
<td>Michael Donovan, MD, PhD</td>
<td>Aureon Laboratories Incorporated</td>
</tr>
<tr>
<td>11:55AM – 12:10PM</td>
<td>Circulating MicroRNAs as Stable Blood-Based Markers for Cancer</td>
<td>Muneesh Tewari, MD, PhD</td>
<td>Fred Hutchinson Cancer Center</td>
</tr>
<tr>
<td>12:10PM – 12:25PM</td>
<td>PCA-3 and Gene Fusion Based Diagnostics of Prostate Cancer</td>
<td>Jack Schalken, PhD</td>
<td>Nijmegen Center for Molecular Life Sciences</td>
</tr>
<tr>
<td>12:25PM – 12:45PM</td>
<td>Discussion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12:45PM – 1:00PM</td>
<td>Closing Comments and RFA Plans for 2009</td>
<td>Jonathan Simons, MD</td>
<td>Prostate Cancer Foundation</td>
</tr>
</tbody>
</table>