



IV. Prostate Cancer Research Program



Vision: To conquer prostate cancer.

Mission: To promote innovative, multidisciplinary, and regionally focused research directed toward eliminating prostate cancer.

Congressional Appropriations for Peer Reviewed Research:

- \$395M in FY97–02
- \$85M in FY03
- \$85M in FY04

Funding Summary:

- 797 awards from the FY97–02 appropriations
- 216 awards from the FY03 appropriation
- ~215 awards anticipated from the FY04 appropriation

*promoting
innovative
research*

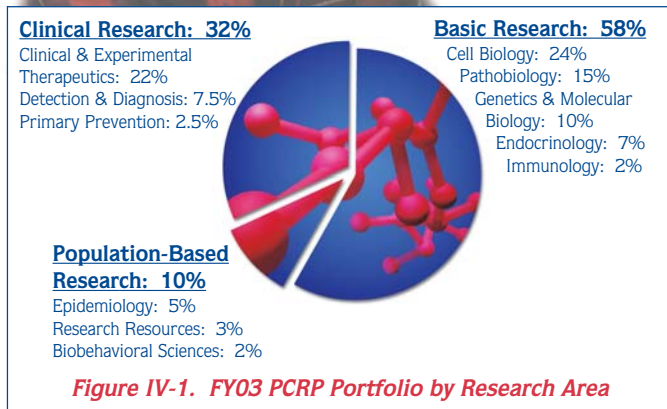


Figure IV-1. FY03 PCR Program Portfolio by Research Area

The Disease

Prostate cancer is the most commonly diagnosed cancer in men, accounting for 33% of all cancers in men. In 2004, approximately 230,110 men in the United States will be diagnosed with prostate cancer and an estimated 29,900 will die from the disease.

Prostate cancer is second only to lung cancer as a leading cause of cancer deaths in men. Prostate cancer incidence rates remain significantly higher in African American men compared to Caucasian men, and the death rate for African American men remains more than twice that of Caucasian men.¹ Currently, there is no cure for locally advanced or metastatic prostate cancer.

Program Background

The Department of Defense (DOD) Prostate Cancer Research Program (PCRP) was established in fiscal year 1997 (FY97) by Appropriations Conference Committee Report No. 104-863, which provided \$45 million (M) for research in prostate cancer. As a major funder of extramural prostate cancer research, the PCRP has managed \$565M from FY97 to FY04 to fund peer reviewed prostate cancer research. A total of 1,013 awards have been made through FY03 to promote innovative, multi-institutional, and multidisciplinary research directed toward conquering prostate cancer. The PCRP believes that building critical resources and collaborations, exploring groundbreaking concepts and ideas, training future leaders, and sponsoring clinical research will ultimately lead to the elimination of prostate cancer (see the box story on pages IV-7–IV-8 for a review of the clinical trials [CTs] supported by the PCRP). Appendix B, Table B-2, summarizes the congressional appropriations and the investment strategy executed by the PCRP for FY03–04.

The Fiscal Year 2003 Program

Congress appropriated \$85M in FY03 to continue the peer reviewed DOD PCRP. As in previous years, the PCRP continued to emphasize innovation and training. The programmatic vision was implemented by requesting proposals in research and training/recruitment. As illustrated in Figure IV-1, the FY03 PCRP has developed a diverse research portfolio that encompasses basic, clinical, and population-based research. Table IV-1 provides a summary of the FY03 PCRP award categories and mechanisms in terms of number of proposals received, number of awards, and dollars invested.

The FY03 PCRP offered nine award mechanisms to support research directed toward eliminating this life-threatening disease. A total of 834 proposals were received, and 216 were funded.

¹ American Cancer Society - *Cancer Facts and Figures*, 2004.

“I am reminded of...all the hard work and brilliant science that has gone into this program [PCRP].”

Phil Olsen, FY04 PCRP Consumer Peer Review Panel Member

The Physician Research Training Award, one of the new award mechanisms in FY03, resulted in the support of five gifted physicians preparing for careers in prostate cancer research through a mentored training experience. The other two new award mechanisms, the Exploration Awards, resulted in 43 funded projects collectively to either develop critical resources or explore groundbreaking concepts in the field of prostate cancer.

The PCRP’s investment in innovative, high-risk/high-gain research resulted in 116 awards (Idea Development and New Investigator Awards). To address the disparate incidence, morbidity, and mortality among African Americans and other ethnic groups, the PCRP supported 13 awards collectively under the Health Disparity Prostate Scholar Awards and the HBCU Collaborative Partnership Award. Finally, a total of 39 talented doctoral graduates were funded under the Postdoctoral Traineeship Award to prepare the future leaders in prostate cancer research.

The Vision for the Fiscal Year 2004 Program

Congress appropriated \$85M to continue the PCRP in FY04. The emphasis for the FY04 program was placed on innovation, training, and the foundation for clinical trials. A total of 883 proposals were received, as shown in Table IV-2, and approximately 215 awards are expected.

Eleven award mechanisms were offered in FY04, nine of which were previously established by the PCRP. The two new mechanisms offered in the FY04 PCRP were as follows:

Table IV-1. Funding Summary for the FY03 PCRP

Category & Award	Proposals	Awards	Investment
Research			
Exploration–Hypothesis Development	121	34	\$3.9M
Exploration–Resource Development	36	9	\$1.0M
HBCU Collaborative Partnership	5	2	\$1.9M
Health Disparity Research–Prostate Scholar Awards	11	9	\$4.3M
Idea Development	392	85	\$46.4M
New Investigator	141	31	\$10.0M
Training/Recruitment			
Health Disparity Training – Prostate Scholar Awards	4	2	\$0.4M
Physician Research Training Awards	8	5	\$3.0M
Postdoctoral Traineeships	116	39	\$3.8M
Total	834	216	\$74.7M

■ The Clinical Trial Development Award was designed to establish and develop collaborations and research resources that will serve as a foundation for clinical trials relevant to prostate cancer treatment, diagnosis, detection, or prevention. Investigators funded under the Clinical Trial Development Award will have the opportunity to compete, along with other eligible applicants, for the Clinical Trial Award in FY05.

■ The HBCU Undergraduate Collaborative Summer Training Program Award was launched to establish summer prostate cancer training programs at host institutions (which include for-profit, non-profit, public, and private organizations) to provide meaningful research experiences for undergraduate students enrolled at HBCU. A goal of this award is to create collaborative relationships between host institutions and HBCU that will ultimately attract talented undergraduate students into careers that focus on prostate cancer research.



Scientific Outcomes and Advances

The PCRP has supported 1,013 studies that focus on prostate-specific research, approximately 300 of which have been completed.

Examination of PCRP award outcomes already reveals how PCRP grantees are pushing the boundaries and advancing discoveries in prostate cancer research. The following highlighted projects represent the research of dedicated investigators working to increase basic knowledge about, prevent, treat, and improve the lives of individuals affected by prostate cancer.

Cholesterol and Prostate Cancer

Michael R. Freeman, Ph.D., Children's Hospital Boston, Boston, Massachusetts

The Emory University Consortium, led by Dr. Jonathan Simons of Emory University's Winship Cancer Center, involves researchers from multiple institutions working together on a variety of projects to identify new therapeutic targets and concepts for treating metastatic prostate cancer. Dr. Michael Freeman's work in the Consortium focuses on "lipid rafts," which are portions of a cell's membrane that contain high concentrations of lipids such as cholesterol. These rafts can function as cell signaling centers allowing information to travel within the cell's environment and activate other genes and pathways in a step-by step fashion. It has long been known that prostate cancer cells accumulate cholesterol, but the implications of this accrual have been unclear. Previously, Dr. Freeman and his colleagues showed that high levels of the cholesterol-rich lipid rafts help prostate cancer cells survive and multiply; survival of the cancer cells was reduced if the lipid rafts were disrupted. In his work in the Emory

Consortium, Dr. Freeman is examining the relationship between circulating cholesterol and malignant prostate cancer and whether cholesterol-reducing agents such as the cholesterol-lowering

"statin" drugs used for heart disease prevention can block the onset of prostate cancer or divert its progression to malignant disease. The characterization of the components of cholesterol-rich lipid rafts found in prostate cancer cells may lead to the identification of new biomarkers for prostate cancer progression and to novel targets for therapeutic intervention.

For additional reading about this research, please refer to the following publications:

- Zhuang L, Lin J, Lu ML, et al. 2002. Cholesterol-rich lipid rafts mediate Akt-regulated survival in prostate cancer cells. *Cancer Research* 62(8):2227–2231.
- Freeman MR, Solomon KR. 2004. Cholesterol and prostate cancer. *Journal of Cell Biochemistry* 91(1):54–69.

From Cosmetic Concerns to Quality of Life: The Journey of Laser Technology in Prostate Cancer Treatment

Nathaniel M. Fried, Ph.D., Johns Hopkins School of Medicine, Baltimore, Maryland

Following prostate cancer surgery, many patients (5%–20%) suffer from urethral and bladder neck strictures. The scarring from the surgery leads to stenosis or a narrowing of the urethra and/or bladder neck and this, in turn, causes urinary incontinence. Traditional methods to treat the strictures such as balloon dilation, cold knife incision, electrocautery, and Holmium laser technology have met with limited success. These failures lead to a

Table IV-2. Award Mechanisms Offered and Proposals Received for the FY04 PCRP

Category & Award	Proposals
Research	
Exploration–Hypothesis Development	162
Exploration–Resource Development	30
HBCU Collaborative Partnership	4
Health Disparity Research–Prostate Scholar Awards	10
Idea Development	419
New Investigator	113
Training/Recruitment	
HBCU Undergraduate Collaborative Summer Training Program	4
Health Disparity Training–Prostate Scholar Awards	2
Physician Research Training Awards	18
Postdoctoral Traineeships	111
Research Resources	
Clinical Trial Development Award	10
Total	883

“The U.S. Army’s CDMRP...has provided a critical opportunity for the scientific community to respond to the challenge by the DOD to conduct translational research...”
Chung Lee, Ph.D., FY04 PCRP Peer Review Panel Member

decrease in the quality of life for prostate cancer survivors. To alleviate one of the major side effects of prostate cancer surgery, Dr. Nathaniel M. Fried and colleagues at the Johns Hopkins School of Medicine in Baltimore, Maryland have utilized a new laser technology in urology. Exploiting methodology in use for painless cosmetic wrinkle removal, Dr. Fried has shown that the Erbium:YAG laser is up to 30 times more precise than the Holmium:YAG laser for urological purposes. Wound healing studies demonstrated that the Erbium laser is capable of producing incisions and opening the urethra with minimal thermal damage to surrounding healthy tissue, which should translate into reduced scarring and recurrence of strictures. Importantly, a major focus of the Fried laboratory has been to devise an optical fiber delivery system. By using the optical fiber system, the Erbium laser energy treatment may be delivered through an endoscope, thus promising a minimally invasive treatment of urinary incontinence. These ongoing studies may lead to hope for millions of men with prostate cancer and increase their quality of life after prostate cancer surgery. This research was made possible with funding from an FY02 PCRP New Investigator Award.

Please refer to the following publications for further information about this research:

- Fried NM, Tesfaye Z, Ong AM, et al. 2003. Optimization of the Erbium:YAG laser for precise incision of ureteral and urethral tissues: In vitro and in vivo results. *Lasers in Surgery and Medicine* 33(2):108–114.
- Chaney CA, Yang Y, Fried NM. 2004. Hybrid germanium/silica optical fibers for endoscopic delivery of Erbium:YAG laser radiation. *Lasers in Surgery and Medicine* 34(1):5–11.

Putting Prostate Cancer Genes on the Map

William B. Isaacs, Ph.D., Johns Hopkins University School of Medicine, Baltimore, Maryland, and Jianfeng Xu, M.D., Wake Forest University School of Medicine, Winston–Salem, North Carolina

Ancestry defines us not only ethnically and culturally but also genetically. Family and ethnic groups, which are more similar genetically than the general population, are important resources in the hunt for genetic causes for diseases as diverse as Huntington’s disease, cystic fibrosis, and breast cancer. Discovering which genes are important in

the development of prostate cancer may lead to similar breakthroughs in our understanding of the causes and development of prostate cancer. The relative importance of the leading genetic variations has not been determined because studies with the general population have not been able to isolate those genes with the greatest impact on prostate cancer development. Several genetic variations identified initially in population-based studies have not demonstrated significance in prostate cancer development in subsequent studies. Drs. Isaacs and Xu are using families at greater risk for prostate cancer to identify specific regions of chromosomes and, ultimately, the genes associated with prostate cancer development in studies funded by three awards from the PCRP. They are using microsatellite markers (small, unique sequences associated with specific locations on each of our 23 chromosomes) to rapidly screen a man’s genome for locations that are similar among men with prostate cancer but differ from the “normal” population. Thus far, Drs. Isaacs and Xu have identified several potential prostate cancer-causing chromosomal regions that may be significant in prostate cancer. Analysis of a set of 36 Ashkenazi Jewish families found that family members with prostate cancer were more likely to have matching microsatellite markers on a portion of chromosome 7 than would be expected by chance. In another study, genetic samples of 126 individuals from 33 African American families with high incidences of prostate cancer provided evidence for five prostate cancer susceptibility regions: three on chromosome 1 (HPC1, PCAP, and CAPB), HPC20 on chromo-

Signs and Symptoms

Signs and symptoms do not typically accompany early cases of prostate cancer. However, some indicators of more advanced prostate cancer include:

- *Frequent urination, especially at night*
- *Weak or interrupted urine flow*
- *Inability to urinate or difficulty starting or stopping the urine flow*
- *Painful or burning sensation when urinating*
- *Blood in the urine*
- *Continual pain in the lower back, pelvis, or upper thighs*

However, most of these symptoms are nonspecific and are not always related to a serious condition.^a

^a *American Cancer Society – Prostate Cancer Fact Sheet and Cancer Facts and Figures, 2004.*

“The DOD PCRIP, since its inception in 1997, has become the single funding agency...to which prostate cancer-specific investigators world-wide turn when they are developing a new idea or concept.”

Nicholas Vogelzang, M.D., FY04 PCRIP IP Chair

some 20, and HPCX on the X chromosome. Finding the chromosomal region linked to inheriting an increased risk for prostate cancer is only the first step; the team is now trying to locate the actual cancer-causing gene(s). Once identified, these genes will be assessed for use in genetic tests to identify men who are at greater risk to develop prostate cancer than the general population. This research was made possible with funding from FY97 and FY02 PCRIP Idea Development Awards.

Additional information about this research can be found in the following two selected publications:

- Brown WM, Lange EM, Chen H, et al. 2004. Hereditary prostate cancer in African American families: Linkage analysis using markers that map to five candidate susceptibility loci. *Br J Cancer* 90(2):510–514.
- Friedrichsen DM, Stanford JL, Isaacs SD, et al. 2004. Identification of a prostate cancer susceptibility locus on chromosome 7q11–21 in Jewish families. *Proc Natl Acad Sci USA* 101(7):1939–1944.

Hyaluronic Acid and Hyaluronidase: Promising Prognostic Indicators for Prostate Cancer

Vinata B. Lokeshwar, Ph.D., University of Miami School of Medicine, Florida

Increased use of the PSA (prostate-specific antigen) test during the last decade has significantly increased the detection of localized disease, which has the potential to be cured by surgery or radiation. Even when treatment appears successful, prostate cancer recurs in many patients with localized disease, and current methods to predict prostate cancer progression are not accurate. Dr. Vinata Lokeshwar developed a test for bladder cancer based on measuring concentrations of hyaluronic acid (HA), a sugar polymer and component of the tissue matrix and fluids, and the enzyme that breaks it down, hyaluronidase (HAase). This work indicated the potential for HA/HAase as an effective tumor marker in bladder cancer. Dr. Lokeshwar's group further examined the possibility that elevated levels of HA/HAase could be a marker for prostate cancer progression based on their understanding that many tumors share similar characteristics of growth and metastasis. They compared the predictive value of HA and HAase with six other biochemical and structural markers of prostate cancer, including PSA

and Gleason score. They found that measuring HA and HAase in combination was 85% accurate in predicting recurrence of prostate cancer. This was superior to any other marker. Predictive accuracy is increased when HA/HAase are combined with information about the tumor margins and extra prostatic extension. Use of these combined prognostic indicators shows great promise in improving doctors' ability to identify localized prostate cancers that are likely to progress and ensuring that these patients receive more aggressive treatment. This research was made possible with funding from an FY01 PCRIP Idea Development Award.

Further information about prognostic markers for metastatic prostate cancer can be found in the following publications:

- Posey JT, Soloway MS, Ekici S, et al. 2003. Evaluation of the prognostic potential of hyaluronic acid and hyaluronidase (HYAL1) for prostate cancer. *Cancer Res* 63:2638–2644.
- Lokeshwar VB, Schroeder GL, Carey RI, et al. 2002. Regulation of hyaluronidase activity by alternative mRNA splicing. *J Biol Chem* 277(37):33654–33663.
- Ekici S, Cerwinka WH, Duncan RC, et al. 2004. Comparison of the prognostic potential of hyaluronic acid, hyaluronidase (HYAL-1), CD44v6 and microvessel density for prostate cancer. *Int J Cancer* 112:121–129.
- Lokeshwar VB, Cerwinka WH, Lokeshwar BL. 2004. HYAL1 hyaluronidase: A molecular determinant of bladder tumor growth and invasion. *Cancer Research*.

Bottom Line

Since 1997, the DOD PCRIP has been responsible for managing \$565M in congressional appropriations, resulting in 1,013 awards from FY97 to FY03. Together, PCRIP-supported investigators have intensified the fight against prostate cancer by making important contributions to understanding, preventing, detecting, diagnosing, and treating this life-threatening disease. Research highlights, award data, and abstracts of funded PCRIP proposals can be viewed on the CDMRP website (<http://cdmrp.army.mil>).

PCRP Clinical Trials Assessment

Since its inception, the PCRP has sponsored clinical research to accelerate the elimination of prostate cancer. In 2004, an assessment was initiated to evaluate the status of PCRP-sponsored CTs funded in FY97–02.

Using the U.S. Food and Drug Administration's (FDA's) definition, which defines a CT as "a prospective study comparing the effect and value of intervention(s) against a control in human subjects," 25 CTs were identified in the FY97–02 PCRP portfolio. In this definition, intervention is used in the broadest sense to include "prophylactic, diagnostic, or therapeutic agents, device regimens, procedures, etc."^a

The 25 CTs identified in the PCRP portfolio comprise approximately 3% of the total number of grants and approximately 4% of the dollars. A total of 40% are Phase 1 trials and 28% are combination Phase 1/2 trials (Figure 1). Phase 2 and Phase 2 randomized CTs represent 20% and 12%, respectively, of the CTs portfolio. Sixty-eight percent of the funded trials involve a treatment, with the remaining trials involving preventives, diagnoses, or behavioral/decision-making support (Figure 2). Finally, 80% of the trials involve a drug (40%), dietary intervention (20%), or a behavioral intervention (20%) (Figure 3).

Of the 25 PCRP-supported CTs, 9 are completed or partially completed, and the remaining 16 are active, waiting for regulatory approvals, recruiting/treating patients, or analyzing data (Figure 4). While most of the PCRP supported CTs are still in their early stages and the impact of them will not be known for a few years, three have already attracted commercial partners for an ongoing clinical study (Millenium, Mederex, and Avantis). Today, the PCRP remains committed to funding a portfolio of clinical research to hasten the campaign against prostate cancer (see The Vision for the Fiscal Year 2004 Program for the PCRP's continued investment in clinical trials). The following projects have been highlighted as having notable outcomes as a direct result of the trial(s).

(90)Y-DOTA-huJ591, Humanized Monoclonal Antibody Specific to the Extracellular Domain of Prostate Specific Membrane Antigen (PSMA): Dose Escalation Trial in Patients with Prostate Cancer

Radioimmunotherapy is a form of cancer treatment that involves delivering radioactive agents directly to tumor cells by using the patient's own immune system. The radioactive agents are attached to antibodies that then travel through the blood stream and bind specifically to proteins on the tumor cell surface. In this way, many antibody molecules can bind to the tumor and deliver a lethal radiation dose. Dr. Shankar Vallabhajosula and researchers at the Cornell University Medical Center are making significant progress in developing radioimmunotherapy as a potential treatment method for prostate cancer. The researchers developed a Yttrium-90 labeled antibody, which binds to the PMSA molecule on prostate cancer cells and tested it in a Phase 1 clinical trial at Memorial Sloan Kettering under joint sponsorship between Millenium Pharmaceuticals and the National Cancer Institute. The targeted therapy was found to be well tolerated and successful in specifically targeting prostate tumors; the maximum tolerated dose (MTD) was determined to be 17.5 mCi/m². Administration of the drug at this dose caused significant antitumor response in two out of four patients with 70%–85% declines in PSA for more than 6 months. Millenium Pharmaceuticals is planning to conduct Phase 2 CTs soon. Part of this research was made possible with funding from FY97 and FY00 PCRP Dual-Phase Idea Development Awards.



Figure 1. Phases of CT Supported in the FY97-02 PCRP



Figure 2. Types of CT Supported in the FY97-02 PCRP



Figure 3. Method of Intervention in the FY97-02 PCRP CT



Figure 4. Status of CTs Supported in the FY97-02 PCRP

^a Friedman LM, Furberg CD, DeMets DL (eds). 1985. *Fundamentals of Clinical Trials*, 2nd ed. St. Louis: CV Mosby.

***Modulation of Paclitaxel Antitumor Effects by Calcitriol:
Preclinical and Clinical Studies of Mechanisms, Toxicity, and Efficacy in Prostate Cancer***

Calcitriol (vitamin D) has been shown to inhibit the growth of normal and cancerous cells in a variety of solid tumor model systems. It has also been shown to inhibit prostate cancer growth in the laboratory. However, administration of calcitriol for the treatment of cancer has been shown to increase blood calcium, which is very toxic. In an effort to develop a new treatment approach for prostate cancer, Dr. Donald Trump and his team formerly at the University of Pittsburgh and now at Roswell Park Cancer Institute (RPCI), tested the combination of calcitriol and paclitaxel (Taxol) in a dose escalation phase 1 CT in 30 patients with advanced prostate cancer. Paclitaxel is a chemotherapeutic agent that has been shown to be effective against ovarian and advanced breast cancers and shows great potential for the treatment of prostate cancer. While an MTD was not reached, escalation was completed through 38 µg calcitriol daily for 3 days weekly + 80 mg/sqm paclitaxel weekly. While myelosuppression was observed, no serum calcium levels greater than 11 mg/dL were observed. The synergism of this combined therapy in preclinical models is important as it offers the potential for the enhancement of a potent antitumor agent (paclitaxel) with what appears to be a very safe regimen of calcitriol. The CT suggests that paclitaxel may reduce the potential for calcitriol-induced hypercalcemia, as the weekly total dose of calcitriol in this trial is almost 12x the usual weekly dose of oral calcitriol. The addition of paclitaxel enhances cell killing by calcitriol, while limiting calcium levels in the blood. The FDA has now approved docetaxel (Taxotere), which like paclitaxel is a taxoid drug, for the treatment of men with androgen-independent prostate cancer. Additionally, Dr. Trump and colleagues at RPCI with the National Cancer Institute (NCI) sponsorship are conducting a phase 2 study of calcitriol and dexamethasone in patients with early, recurrent prostate cancer after prior radical prostatectomy or radiotherapy as well as studies of calcitriol administered intravenously either with docetaxel or gefitinib (Iressa). Part of this research was made possible with funding from an FY97 PCRP Idea Development Award.

Daily 1(alpha)-OH-D(2) in Hormone Refractory Prostate Cancer Assessment of Clinical and Biochemical Effects

1(alpha)-OH-D(2) (doxercalciferol) is a synthetic derivative of vitamin D that has been shown to inhibit the growth of cancer but with less of an effect on increasing calcium levels in the blood. Dr. Howard Bailey and researchers at the University of Wisconsin have been testing doses of doxercalciferol in prostate cancer patients. In Phase 1 of this trial, the safe dose of doxercalciferol in patients with hormone refractory prostate cancer was determined to be 12.5 µg per day. Using this dose, the Phase 2 study showed that 6 of 26 patients with hormone refractory prostate cancer had stable disease for longer than 6 months. Toxicity was minimal except for a few cases of hypercalcemia and increased creatinine levels. Currently, an NCI Phase 2 randomized study comparing docetaxel alone versus docetaxel plus doxercalciferol in patients with localized prostate cancer is ongoing at the University of Wisconsin. Part of this research was made possible with funding from an FY97 PCRP Idea Development Award.

Fiscal Year 2004 Integration Panel Members

Nicholas Vogelzang, M.D. (Chair), Nevada Cancer Institute

Frederic Waldman, M.D., Ph.D. (Chair Emeritus), University of California at San Francisco

Robert Dreicer, M.D. (Chair-Elect), The Cleveland Clinic Foundation

Gail Prins, Ph.D. (Executive Committee, Member-at-Large), University of Illinois at Chicago

Virgil Simons (Executive Committee, Member-at-Large), The Prostate Net

Thomas Carey, Ph.D., University of Michigan Comprehensive Cancer Center

Jean deKernion, M.D., Los Angeles School of Medicine

Ronald Lieberman, M.D., National Cancer Institute

Monica Liebert, Ph.D., American Urological Association

Timothy Ratliff, Ph.D., University of Iowa

Mack Roach, III, M.D., University of California at San Francisco

Joseph Smith, Jr., M.D., Vanderbilt University School of Medicine

Howard Soule, Ph.D., Prostate Cancer Foundation

Wendell Van Auken, M.B.A., University of California at San Francisco Cancer Center