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Abstract

The Dean and Betty Gallo Prostate Cancer Center (GPCC) was established with the goal of eradicating prostate cancer and improving the lives of men at risk for the disease through research, treatment, education and prevention. GPCC was founded in the memory of Dean Gallo, a beloved New Jersey Congressman who died tragically of prostate cancer diagnosed at an advanced stage. GPCC unites a team of outstanding researchers and clinicians who are committed to high-quality basic research, translation of innovative research to the clinic, exceptional patient care, and improving public education and awareness of prostate cancer. GPCC is a center of excellence of The Cancer Institute of New Jersey, which is the only NCI-designated comprehensive cancer center in the state. GPCC efforts are now integrated well as part of our Prostate Program at CINJ, in which Dr. Robert DiPaola and Dr. Cory Abate-Shen are co-leaders.

The Prostate Program unites 19 investigators from 10 academic departments who have broad and complementary expertise in prostate cancer research. The overall goal and unifying theme is to elucidate basic mechanisms of prostate growth and oncogenesis, with the ultimate goal of promoting new and effective strategies for the eradication of prostate cancer. Members' wide range of research interests collectively optimize the chances of providing new insights into normal prostate biology and unraveling the molecular pathophysiology of prostate cancer. Cell culture and powerful animal models developed by program members recapitulate the various stages of prostate cancer progression, including prostatic intraepithelial neoplasia, adenocarcinoma, androgen-independence, invasion and metastases. These models promise to further strengthen an already robust program of investigator-initiated therapeutic clinical trials, including studies adopted by national cooperative groups. Efforts to translate laboratory results into clinical studies of early detection and chemoprevention are underway.

The specific goals of this program are:

1. To investigate the molecular mechanisms underlying normal prostate growth and differentiation and elucidate the molecular mechanisms underlying prostate oncogenesis.
2. To build on fundamental knowledge to develop effective therapeutic approaches for the treatment of prostate cancer.
3. To improve the control of prostate cancer through early detection, chemoprevention, and outreach and education.

This new disease-based program is structured to improve interdisciplinary interactions and translational results. Already, through the dynamic leadership of Drs. Cory Abate-Shen and Robert DiPaola, new investigators were attracted to the field, new collaborations engendered, and numerous investigator-initiated trials implemented.

Progress in GPCC and the program overall has been outstanding. The Center has success in uniting investigators with broad and complementary expertise in prostate cancer research. The overall goal and unifying theme is to elucidate basic mechanisms of prostate growth and oncogenesis, with the ultimate goal of promoting new and effective strategies for the eradication of prostate cancer in patients and populations at risk. Members' wide range of research interests collectively optimize the chances of providing new insights into normal prostate biology and unraveling the molecular pathophysiology of prostate cancer. Studies in cell culture and powerful animal models developed recapitulate the various stages of prostate cancer progression, including prostatic intraepithelial neoplasia, adenocarcinoma, androgen-independence, invasion and metastases. These

models promise to further strengthen an already robust program of investigator-initiated therapeutic clinical trials, including studies adopted by national cooperative groups. Efforts to translate laboratory results into clinical studies of early detection and chemoprevention are underway.

PROSTATE CANCER PROGRAM
DOE FINAL Report
Program Co-Leader: Cory Abate-Shen, Ph.D.
Program Co-Leader: Robert DiPaola, M.D.

Program Members

Investigator	Department
Cory Abate-Shen, Ph.D.	Neuroscience and Cell Biology (RWJMS)
Paul Copeland, Ph.D.	Molecular Genetics, Microbiology and Immunology (RWJMS)
Steven DiBiase, M.D.	Radiation Oncology (RWJMS)
Robert DiPaola, M.D.	Medicine (RWJMS)
Joseph Fondell, Ph.D.	Physiology and Biophysics (RWJMS)
Ramsey Foty, Ph.D.	Surgery (RWJMS)
William N. Hait, M.D., Ph.D.	Medicine and Pharmacology (RWJMS)
Diane Heck, Ph.D.	Pharmacology and Toxicology (RU)
Longqin Hu, Ph.D.	Pharmaceutical Chemistry (RU)
Jeffrey Laskin, Ph.D.	Environmental and Community Medicine (RWJMS)
Grace Lu-Yao, Ph.D.	Environmental and Community Medicine (RWJMS)
Ronald Morton, Jr., M.D.	Surgery (RWJMS)
John Pintar, Ph.D.	Neuroscience and Cell Biology (RWJMS)
Arnold B. Rabson, M.D.	Molecular Genetics, Microbiology and Immunology (RWJMS)
Danny Reinberg, Ph.D.	Biochemistry (RWJMS)
Monica Roth, Ph.D.	Biochemistry (RWJMS)
Armen Sarvazyan, Ph.D.	Surgery (RWJMS)
Michael Shen, Ph.D.	Pediatrics (RWJMS)
Mark Stein, M.D.	Medicine (RWJMS)
Mary B. Todd, D.O.	Medicine (RWJMS)
Robert Weiss, M.D.	Surgery (RWJMS)

Scientific Goals

GPCC and the program overall has success in uniting investigators with broad and complementary espertise in prostate cancer research. The Prostate Program unites investigators with broad but complementary expertise in prostate cancer research. The overall goal and unifying theme is to elucidate basic mechanisms of prostate development and oncogenesis, with the ultimate goal of promoting new and effective strategies for the eradication of prostate cancer. Members have a wide range of research interests that collectively optimize the chances of providing new insights into normal prostate biology, as well as unraveling the molecular pathophysiology of prostate cancer. Studies in cell culture systems and animal models recapitulate the various stages of prostate cancer progression, including prostatic intraepithelial neoplasia, adenocarcinoma, androgen-independence, invasion and metastases. These models promise to strengthen the already robust menu of investigator-initiated therapeutic and preventive clinical trials, including studies adopted by national cooperative group. Efforts to tranlate laboratory results into clinical studies of early detection and chemoprevention are underway.

The specific goals of this program are:

1. To investigate the molecular mechanisms underlying normal prostate growth and differentiation and elucidate the molecular mechanisms leading to prostate cancer.
2. To build on fundamental knowledge to develop effective therapeutic approaches for the treatment of prostate cancer.
3. To improve the control of prostate cancer through early detection, chemoprevention, outreach and education.

Scientific Accomplishments

Members of the Prostate Program made important contributions in each of the main focus areas. These accomplishments are summarized below.

1. To investigate the molecular mechanisms underlying normal prostate growth and differentiation and elucidate the molecular mechanisms leading to prostate cancer.

RATIONALE/CANCER FOCUS: Through a fundamental understanding of prostate biology gleaned from a combination of *in vivo* and *in vitro* approaches, program members are making important inroads into understanding the pathways of prostate cancer initiation and progression. One of the principal accomplishments of the Prostate Program is the generation of new mouse models of prostate cancer. These models stimulated a broad range of multidisciplinary studies on the mechanisms of prostate cancer development, the elucidation of molecular events associated with disease progression, and have the potential for developing new paradigms for prevention and treatment. Summarized below are examples of these research accomplishments.

ACCOMPLISHMENTS: The collaborative efforts of Cory Abate-Shen and Michael Shen elucidated a critical role for the *Nkx3.1* homeobox gene in the development of the normal prostate and how defects in its expression contribute to the development of prostate cancer. GPCC has supported the development of the transgenic mouse core facility at CINJ. They demonstrated that *Nkx3.1* is the earliest known marker of prostate formation and that it is required for appropriate prostate morphogenesis and epithelial differentiation. These studies were accelerated by their creation of mutant mice with loss-of-function of *Nkx3.1*. Using transcriptional profiling of normal and mutant mouse tissues, they are uncovering the mechanisms by which *Nkx3.1* regulates prostatic epithelial differentiation. For example, they found that *Nkx3.1* mutants express genes that are usually restricted to seminal vesicles, suggesting that loss-of-function of *Nkx3.1* leads to defects in prostatic epithelial specification. They hypothesized that these defects in specification predispose *Nkx3.1* mutant mice to malignant transformation of the prostate. These studies provide important insights linking the control of differentiation to mechanisms underlying oncogenesis, as well as the role of homeobox genes in these processes (Abate-Shen, *Nat Rev Cancer,* 2002; Abate-Shen, *Cancer Cell,* 2003; Shen and Abate-Shen, *Dev Dyn,* 2003).

Shen applied his expertise in vertebrate development using mouse models (Ding et al., *Nature,* 1998; Yan et al., *Genes Dev,* 1999; Schier and Shen, *Nature,* 2000; Iratni et al., *Science,* 2002; Morkel et al., *Development,* 2003; Shen, *J Clin Invest,* 2003) to the study of prostate biology (Bhatia-Gaur et al., *Genes Dev,* 1999). He generated mice carrying an *Nkx3.1-lacZ* knock-in allele, which enabled him to develop a novel explant culture system that supports the reproducible growth and differentiation of prostatic epithelium *in vitro* (*Dev. Bio.,* 2003, in press). Dr. Shen and colleagues used this assay to quantify the formation of prostatic ducts in explant cultures using embryonic tissues that normally give rise to prostate from wild-type and mutant mice. This assay can be adapted for rapid screening of therapeutics agents that affect prostatic growth. In collaboration with Dr. Philip Beachy's laboratory at John's Hopkins, they found that inhibition of sonic hedgehog (Shh) signaling had adverse consequences for prostate morphogenesis. Their studies also demonstrated that defects in prostate morphogenesis in *Shh* mutants is an indirect consequence of a partial deficiency in androgen production; *Shh*

does not appear to be essential for prostate induction, but is required for prostate morphogenesis. Given the importance of aberrant Shh signaling in other cancers, these findings suggest a role for this signaling pathway in the genesis of prostate cancer.

Signaling through the insulin-like growth factor (IGF) pathway became an entry point for **John Pintar** into prostate cancer research. Pintar investigates the role of IGF binding proteins (IGF-BPs) in normal growth and development using mutant mouse models generated in his laboratory (Pintar et al., *Prog Growth Factor Res,* 1995; Pintar et al., *Horm Res,* 1996; Grewal et al., *Horm Metab Res,* 1999; Wood et al., *Mol Endocrinol,* 2000; Nitsche et al., *J Neurosci,* 2002; Clarke et al., *Neuroscience,* 2003; Nitsche and Pintar, *Dev Biol,* 2003). Inspired by work of others, who had shown that serum levels of IGF were linked to prostate cancer risk in humans, he applied for and received funding from CINJ Developmental Funds to explore the consequences of loss-of-function of IGF-BPs in prostate cancer. He found that IGF-BP mutant mice displayed hyperplasia and dysplasia of the prostate that was consistent with a pre-cancerous phenotype. He is now investigating whether this phenotype can be exacerbated by combinatorial mating with prostate-cancer-prone strains, such as *p53*, *Pten*, and *Nkx3.1* through collaborations with Abate-Shen and other program members.

Understanding androgen-mediated signal transduction is essential to our knowledge of basic prostate biology and to the pathophysiology of prostate cancer. Joseph Fondell was newly recruited to the faculty and to the field of prostate cancer research to apply his expertise on androgen receptor (AR) physiology to the study of prostate cancer. His laboratory developed a unique series of cell lines that express an epitope-tagged AR to isolate interacting proteins that are likely to regulate transcriptional activity (Wang and Fondell, *Anal Biochem,* 2001; Sharma and Fondell, *Proc Natl Acad Sci U S A,* 2002; Zhang et al., *Oncogene,* 2002). Dr. Fondell demonstrated that AR interacts with the TRAP/Mediator protein, which was first identified as a transcriptional co-activator for another nuclear hormone transcription factor (Sharma and Fondell, *Proc Natl Acad Sci U S A,* 2002). Using chromatin immunoprecipitation assays to define interactions with chromatin templates in cell culture, he found that components of the TRAP complex interact with AR on androgen-responsive promoters in LNCAP prostate cancer cells. Fondell is testing the hypothesis that one of the mechanisms underlying the transition from androgen-dependence to androgen-independence in prostate cancer involves the potential of AR to associate with distinct protein complexes in androgen-responsive versus non-responsive cells. He is collaborating with Danny Reinberg to investigate chromatin assembly in prostate cancer, and with Shen to develop mice having epitope-tagged versions of AR to investigate AR-associated proteins *in vivo* as a function of prostate cancer progression.

Reinberg, an international leader in the field of transcriptional regulation, recently embarked on prostate cancer research through his interest in factors that alter chromatin structure and regulate gene expression (Kuzmichev et al., *Genes Dev,* 2002; Nishioka et al., *Genes Dev,* 2002; Nishioka et al., *Mol Cell,* 2002; Belotserkovskaya et al., *Science,* 2003; Friedl et al., *Proc Natl Acad Sci U S A,* 2003; Saunders et al., *Science,* 2003). His laboratory isolated PRC2 from HeLa cells and found that it methylated lysine-27 on the histone H3 tail. They found that the enzymatic activity of PRC2 resides in a polypeptide termed Enhancer of Zeste (Ezh2). Ezh2, like most other histone lysine methyltransferases (HKMTs), PRC2 contains a SET domain that is an evolutionarily conserved sequence motif identified in the *Drosophila* PEV (position effect variegation) suppressor SU(VAR)3-9, the *Polycomb*-group protein Enhancer of Zeste, and the *trithorax*-group protein Trithorax. Work Reinberg and others demonstrated that this class of protein establish a restrained state of transcriptional repression during development, whereas perturbations of this system can have profound consequences for cancer cells. Reinberg became interested in the potential role of Ezh2 in prostate cancer based on studies reported by others in which gene expression profiling revealed a correlation of Ezh2 expression and the development of prostate cancer. He is collaborating with Dr. Shen to develop mutant mouse models for Ezh2 to investigate its role in the development of prostate cancer. Dr. Reinberg, working in collaboration with Abate-Shen, recently found that Ezh2 overexpression is inversely correlated with methylation of lysine-27 in prostate tissues. These data have important implications for the mechanisms by which Ezh2 contributes to prostate cancer.

Activation of the transcription factor NF–κB leads to expression of several genes and an array of biological consequences including resistance to apoptosis and stimulation of cell proliferation. Arnold Rabson received GPCC Developmental Funds to apply his expertise in this areas to the study of prostate cancer. In collaboration with Celine Gelinas (Transcriptional Regulation and Oncogenesis Program), they found that NF-κB is constituitively activated in androgen-independent prostate cancer cells but not in androgen-dependent cell lines. Evidence of nuclear localization of NF-κB protein, indicative of activation, was also identified in tumor tissue samples of intermediate-grade prostate adenocarcinoma obtained through the CINJ Tissue Retrieval Service (Suh et al., *Prostate,* 2002). Studies in Rabson's laboratory are currently directed at defining the mechanisms responsible for constitutive activation of NF-κB and the consequences of this activation for the development and treatment of prostate cancer. He is collaborating with clinical scientists to develop therapeutic approaches to inactivate NF-κB in several forms of malignancy including prostate cancer.

Ramsey Foty developed novel explant assays to investigate how the biophysical properties of prostate cells correlate with their invasive potential. He used tissue surface tensiometry (TST), a novel *in vitro* method that measures elasticity, viscosity, and cohesivity (Dugay et al., *Dev Biol*, 2003; Robinson et al., *J. Cell Sci*, 2003; Ryan et al., *Proc Natl Acad Sci USA*, 2001; Foty and Steinberg, *Int J Dev Biol*, 2004a; Robinson et al, *Mol Biol Cell*, 2004; Winters et al., *Int J Cancer*, 2004). For comprehensive reviews see Foty and Steinberg, Int J. Dev Biol, 2004a and 2004b. They compared normal and malignant prostate to determine whether TST is an accurate predictor of the invasive potential of prostate tumors, how changes in the tumor microenvironment influence biophysical and invasive properties, and how changes in stromal components, including smooth muscle cells and fibroblasts, influence the elastic and viscous properties of tumors. Foty's lab demonstrated that invasive behavior of prostate carcinoma cell lines is correlated with tumor cohesivity as measured by TST (Foty et al., *Surgical Forum,* 1999). They also established a 3D *in vitro* co-culture system used to investigate the degree and rate of compaction of invasive cancer cells. They demonstrated that the degree of compaction is correlated with increased aggregate cohesivity as measured by TST. These assays are being adapted for rapid and quantitative approaches to address how potential therapeutic agents affect the biophysical properties of prostate cancer cells, and thereby affect invasive potential.

In the burgeoning field of gene therapy, a major limitation is the ability to control delivery of therapeutic genes specifically to cancer cells, since these vectors are often designed to produce cell death. Monica Roth's laboratory established a novel approach to the design of retroviral vectors for specific delivery into prostate cancer (Bupp and Roth, *Mol Ther,* 2002; Bupp and Roth, *Hum Gene Ther,* 2003). She is taking advantage of the fact that retroviral entry into cells is controlled by the surface envelope (Env) protein, which can be altered by replacement of a ten amino acid peptide sequence in the cell-targeting region. By screening libraries of retroviral Env proteins with random peptides substituted into this region, she identified novel Env isolates that efficiently deliver a gene to PC-3 human prostate tumor cells. These "designer" Env proteins will be important reagents in the development of gene therapy for prostate cancer and other malignancies.

Abate-Shen and Shen developed a series of mouse models that recapitulate the stages of prostate epithelial transformation (Bhatia-Gaur et al., *Genes Dev,* 1999; Abate-Shen and Shen, *Genes Dev,* 2000; Abate-Shen, *Nat Rev Cancer,* 2002; Abate-Shen and Shen, *Trends Genet,* 2002; Kim et al., *Cancer Res,* 2002; Kim et al., *Proc Natl Acad Sci U S A,* 2002; Abate-Shen et al., *Cancer Res,* 2003). Their efforts were accelerated through a grant from the Mouse Models of Human Cancer Consortium. These models are based on the loss-of-function of three genes implicated in human prostate cancer; the *Nkx3.1* homeobox gene, the *Pten* tumor suppressor gene, and the $p27^{kip1}$ cell-cycle regulatory gene. *Nkx3.1* single-mutant mice provide a model for prostate cancer initiation and were used to develop a novel assay to investigate the precursor-product relationship of prostate intraepithelial neoplasia (PIN) to cancer (Bhatia-Gaur et al., *Genes Dev,* 1999; Kim et al., *Cancer Res,* 2002). These mutant mice provided important insights into the molecular mechanisms underlying the earliest stages of prostate cancer development and give investigators access to tissues that are difficult to consistently obtain from humans. These models display features of the human disease and provide insights into prostate cancer causation. For example, Abate-Shen and Shen recently found that loss-of-function of *Nkx3.1* leads to increased

oxidative damage to prostatic epithelium as a function of aging. Therefore, *Nkx3.1* mutants provide a model to study the consequences and prevention of oxidative damage with naturally occurring antioxidants. During the next grant period this approach will be carried out in collaboration with Jeffrey Laskin and members of the Carcinogenesis and Chemoprevention Program.

By breeding compound mutant mice with loss-of-function of *Nkx3.1, Pten,* and/or $p27^{kip1}$, Abate-Shen and Shen produced models that ultimately progresses through localized adenocarcinoma to invasion and metastases (Kim et al., *Proc Natl Acad Sci U S A,* 2002; Abate-Shen et al., *Cancer Res,* 2003). Cancer progression in these mice increased with age, and the invasive tumors displayed morphological features highly reminiscent of human prostate cancer. Moreover, androgen-ablation led to androgen-independent prostate cancer and distant metastases. Thus, depending on the specific gene deletion and age of the mouse examined, these mutant mice provide pre-clinical models for studying chemoprevention, angio- and lymphangiogenesis, and for testing new chemotherapeutic agents. For example, ongoing studies being conducted in collaboration with DiPaola, examine the effectiveness of calcitriol for chemoprevention in mice and man. Other studies are planned to investigate the consequences of inhibiting Akt function in the acquisition of an androgen-independent phenotype (*vide infra*).

Shen is developing new mouse models for tracking tumor growth and metastases using high-resolution imaging. This strategy entails generation of a knock-in targeting allele to serves as a permanent imaging marker for tracking prostatic epithelial cells, thereby allowing investigators to follow tumor growth as well as emerging metastases. These mouse models facilitate studies designed to understand the biology behind tumor invasion, as well as the molecular events that allow transformation from androgen-dependent to independent-growth. Imaging approaches will enable more efficient drug testing, since they will permit investigators to asses the effects of treatment without sacrificing the animals.

Therefore members of the Prostate Program supported by the GPCC include some of the nation's leaders in understanding the molecular changes that underlie the development of normal and abnormal prostatic epithelium. They have identified fundamental aspects of signaling pathways and transcription factors whose dysfunction may underlie prostate carcinogenesis. Members generated a unique series of models, summarized in Table 1; these permit investigation of all stages of prostate cancer development and enable investigators to study the molecular biology of disease progression. These models are also being used for pre-clinical studies to design effective strategies for therapy (Aim 2) and prevention (Aim 3). The Prostate Program recruited basic researchers, including those who were not previously involved in disease-based research, to study prostate cancer. We anticipate that during the next grant period this work, aimed at analyzing prostate growth and development, mechanisms of transcriptional control, and other fundamental aspects of prostate biology, will continue to inform studies on prostate cancer pathophysiology.

Table 1. • Mouse Models of Prostate Cancer Developed by Program Members			
STAGE	**MODELS**	**POTENTIAL USES**	**THERAPEUTIC TRIALS PLANNED OR IN PROGRESS**
Pre-disposition to cancer (hyperplasia, dysplasia, and low-grade PIN)	Nkx3.1 mutants IGF-BP mutants	Design of new chemoprevention approaches; identification of prognostic indicators for patients at risk for prostate cancer.	Effectiveness of green tea for preventing prostate cancer (planned); role of dietary factors in cancer initiation (planned): role of oxidative damage in carcinogenesis (ongoing).
Early stages of cancer progression (high-grade PIN; carcinoma in situ)	IGF-BP/p53 compound mutants; "young" Nkx3.1/Pten compound mutants	Design of new chemo-prevention approaches; identification of prognostic indicators for early-stage disease	Effectiveness of calcitriol in cancer prevention (ongoing); consequences of androgen-signaling for cancer progression (ongoing).
Overt carcinoma (locally invasive adenocarcinoma)	HMGA2 transgenic mice; aged Nkx3.1/Pten compound mutants	Design of new anti-cancer drugs; identification of pathways of progression	Consequences of using combinations of 2-deoxyglucose or mTOR inhibitors (planned).
Advanced disease (androgen-independence and metastases)	Androgen-ablated Nkx3.1/Pten compound mutants	Design of new chemotherapeutic approaches; identification of molecular correlates that distinguish androgen-dependent and independent stages of disease.	Androgen-ablation combined with mTOR inhibition and/or 2-deoxyglucose (planned).

2. To build on fundamental knowledge to develop effective therapeutic approaches for the treatment of prostate cancer.

RATIONALE/CANCER FOCUS: The Prostate Program strives to develop the biological basis for more effective methods of treatment and prevention. Program members design and conduct mechanistic-based clinical trials built on both laboratory findings and clinical observations. Members also provide national leadership to improve the treatment of prostate cancer. The mechanisms underlying the development of prostate cancer and the progression from *in situ* to invasive disease and then from hormone-sensitive to hormone-resistant disease are themes that are being analyzed. Investigators pursued the molecular mechanisms of drug resistance, developed strategies to circumvent resistance with early therapy, and used novel approaches to abrogate resistance mechanisms. Summarized below are examples of these research accomplishments.

ACCOMPLISHMENTS: As elegantly demonstrated by many studies in human prostate cancer, as well as the cell culture and mutant mouse models described in Aim 1, the development of neoplastic prostate epithelium results from progressive alterations of pathways that regulate normal cell growth and differentiation. Program members conduct studies in parallel to determine if this progression pathway can provide insights into mechanism of drug resistance. For example, William Hait worked with DiPaola to understand the basis for the refractory nature of prostate cancer to therapy. The CINJ Tissue Retrieval Service enabled the study of sequential expression of drug-resistance gene products in 95 human prostate cancer specimens obtained from patients who had not received hormonal treatment or chemotherapy (Sullivan et al., *Clin Cancer Res,* 1998). As benign glandular epithelium progressed through low-stage, low-grade prostate neoplasia to high-grade, high-stage disease, there was a serial increase in expression of several determinants of drug resistance. Notably, they found evidence for p53 mutations in 15-20% of early prostate cancers that markedly increased with advancing stage and grade of disease. In addition, this work suggested that p53 might regulate the expression of determinants of drug sensitivity such as topoisomerase II-α and the multidrug resistance protein gene, *MRP1*. They went on to show

that *MRP1* is transcriptionally regulated by p53 (DiPaola and Aisner, *Semin Oncol,* 1999; Sullivan et al., *J Clin Invest,* 2000; Yang et al., *Mol Cancer Res,* 2003) and that MRP1 protein decreased accumulation and increased efflux of the antiandrogens, but had no effect on dihydrotestosterone accumulation; *a posteriori* evidence that in the face of p53 mutation and MRP overexpression, androgens might reach their receptors but anti-androgens might not. These results provided a mechanistic basis for the expectation that the use of chemotherapy late in the course of disease would be hampered by a panoply of drug resistance mechanisms and defined a previously unexpected mechanism of resistance to both chemotherapy and antiandrogen therapy in prostate cancer patients who had received neither form of treatment (DiPaola, *Semin Oncol,* 1999; Grzywacz et al., *Cancer Res,* 2003).

These data and other findings challenged the conventional wisdom that chemotherapy ought be used only after hormone ablation, and raised the hypothesis that early chemotherapeutic treatment of prostate cancer may lead to better outcomes. Therefore, DiPaola, Goodin and Todd conducted a series of chemotherapy-based clinical trials in patients before the initiation of hormonal therapy that included a series of laboratory correlates conducted in the DiPaola laboratory funded by several NCI R03 grants (DiPaola et al., *Clin Cancer Res,* 1997; DiPaola, *Semin Oncol,* 1999; DiPaola et al., *J Clin Oncol,* 1999; DiPaola et al., *Cancer,* 2001; Thalasila et al., *Cancer Chemother Pharmacol,* 2003). These investigator-initiated studies focused on patients with progression of disease based on increasing PSA who had not received hormonal therapy (Table 2). For example, mitoxantrone was studied in this early patients population and p53, bcl-2 and topoisomerase expression was assessed in available tumor samples (DiPaola et al., *Cancer,* 2001). Although the clinical activity of this agent was not strikingly different from historical data for treatment of more advanced disease, this trial laid the groundwork for studies of potentially more active and targeted agents in previously untreated patients.

Several additional lines of evidence suggested that p53 status may predict sensitivity to chemotherapy. In collaboration with Eileen White and Arnold Levine (Molecular Mechanisms of Tumor Growth), the Hait laboratory found that the functional status of p53 was closely associated with vinca alkaloid (e.g. vinblastine and vincristine) and taxane (e.g. paclitaxel) sensitivity. Whereas cells with wild-type p53 were relatively sensitive to vincas and resistant to taxanes, those with mutant p53 showed the opposite profile. They demonstrated that the expression of microtubule associated protein 4 (MAP4) was regulated by the transcriptional status of p53. Cells with mutant-p53 had increased expression of MAP4, increased polymerization of microtubules, and increased binding and sensitivity to taxanes (Zhang et al., *Oncogene,* 1998). In related studies, members of the Cancer Pharmacology/ Developmental Therapeutics and Breast Cancer Research Programs investigated the activity of epothilone B, a novel microtubule stabilizing agent whose transport is not affected by ATP Binding Cassette family transporters such as MRP1 or P-glycoprotein. DiPaola and White studied p53 status as a marker of sensitivity to epothilone B and demonstrated that this microtubule stabilizer was more cytotoxic to cells with mutant p53 (Ioffe et al., *Proc Amer Assoc Cancer Res,* 2003), consistent with the observations with taxanes. Based on these findings, DiPaola initiated a study of epothilone and estramustine in hormone-refractory prostate cancer (Table 2) and received Cancer Treatment Evaluation Program (CTEP)-approval for developing this approach through ECOG. In this study the status of p53, MAP4 and MRP will be assayed to determine if they predict sensitivity to epothilones in the clinic.

DiPaola, Hait and White also demonstrated that overexpression of bcl-2 in model systems developed by the White laboratory blocked the collateral sensitivity to taxanes seen in p53 mutant cell lines. Since overexpression of bcl-2 had been observed in earlier studies of human prostate cancer specimens, DiPaola designed studies to abrogate this antiapoptotic mechanism. He identified cis-retinoic acid and alpha-interferon (CRA/IFN) as potent bcl-2 modulators that restored the sensitivity to taxanes in cell lines with mutant p53 and bcl-2 overexpression. He then carried out translational studies including an initial pilot study of the modulators alone in patients with prostate cancer (DiPaola et al., *Clin Cancer Res,* 1997; DiPaola and Aisner, *Semin Oncol,* 1999), followed by a series of phase 1 studies in combination with chemotherapy *(DiPaola et al., J Clin Oncol, 1999; DiPaola et al., Hematol Oncol Clin North Am, 2001; Thalasila et al., Cancer Chemother Pharmacol, 2003).* These initial trials were funded by two R03 grants to DiPaola (CA77135; CA80654). The use of CRA/IFN was adopted by ECOG through a phase II study of CRA/IFN and paclitaxel in patients with

hormone-refractory prostate cancer (E3899). An additional study based on these early findings is a DOD-funded, investigator-initiated trial of retinoic acid, alpha-interferon, taxotere, and estramustine ongoing at CINJ (DOD DAMD17-02-1-0229, PI:DiPaola). DiPaola's laboratory was the reference laboratory for measuring the effects of treatment on bcl-2 and other molecular correlates for the ECOG studies.

Recently, work by DiPaola and White has resulted in a DOD Idea Grant award (DOD W81XWH-05-1-0036). This was based on prior studies that demonstrated the dependence of early tumor growth and progression on anaerobic metabolism through glycolysis. In fact, the preference for tumor cells to depend on glycolysis over normal cells is the basis for the successful development of FDG-PET imaging. Despite these prior data, clinical development of agents that target glycolysis has been limited with initial concern over the lack of a therapeutic window. However, more recent studies have demonstrated that abnormal growth factor and apoptotic pathways, required by tumor cells to resist multiple insults, can drive tumor cells to even further dependence on glycolysis, supporting a rationale for selectivity of abrogating glycolysis in tumor cells compared to normal cells. For example, studies have recently demonstrated that activation of Akt kinase, which occurs commonly in tumor such as prostate cancer that are PTEN deficient, increases dependence of glycolysis. To test agents capable of abrogating the induction of glycolysis, we set up a laboratory co-culture model that could detect the growth effect of autocrine stimulation by tumor cells. Using two dimensional (2D) in-gel electrophoresis (DIGE) and Mass spectrometry, we found that initial changes consisted exclusively of induction of multiple glycolytic enzymes (Dvorzhinski et al., *Proteomics*, 2004). To determine if specific molecular mechanisms are dependent on the induction of glycolysis, we created isogenic cell lines derived from rat prostate epithelial cells transformed with both the adenovirus E1A protein to disrupt RB and a dominant negative form of p53, p53 DD (inactivation of RB and p53 pathways are sufficient for transformation and immortalization of primary rodent epithelial cells) in the laboratory of Dr. E. White. Into this genetic background we have introduced a Bcl-2 expression vector along with a constitutively active form of Akt, myr-Akt, H-Ras, and K-Ras. We have already began to test 2-deoxyglucose, an inhibitor of glycolysis, and found we could decrease the expression of glycoltyic enzymes in the co-culture model, inhibit cell growth at concentrations below what can be obtained safely in humans, and have cytotoxicity independent of Bcl-2 overexpression and Akt activation. The co-culture model and isogenic cell lines form a basis to continue further laboratory and clinical studies to determine the optimal approach to abrogation of glycolysis and mechanisms of sensitivity to such modulation.

Table 2. • Investigator-Initiated Therapeutic Trials in Prostate Cancer

TRIAL	STATUS	LABORATORY BASIS AND CORRELATE	N	COLLABORATORS
Early-Stage/Hormone-Naive Prostate Cancer				
Phase I study of taxotere and radiation in high-risk localized disease	Completed; *ASCO Proceedings*, #772, 2002; *J. Clin Oncol*, 2004)	n/a	30	Kumar DiPaola Weiss
Assessment of molecular markers of drug resistance	Completed; (Sullivan et al., *Clin Cancer Res*, 1998)	p53, bcl-2, MRP,	98	Hait, Amenta
Phase II study of 13 cis retinoic acid and alpha-interferon (CRA/IFN)	Completed; *(DiPaola et al., Clin Cancer Res, 1997)*	Serum TGF-beta and IGF-1	30	DiPaola Weiss Cummings
Serum PK activity with androgen naïve patients	Completed; (Cvijic et al., *Clin Cancer Res*, 2000)	PK activity in serum	14	Chen DiPaola
Phase II study of mitoxantrone	Completed; (DiPaola et al., *Cancer*, 2001)	Bcl-2, p53, and topo II	23	DiPaola, Weiss Todd
Phase II study of onconase and tamoxifen	Completed; *(Eid et al. Urol Res*, 2001)	Serum IGF-1 and TGFbeta	13	DiPaola, Weiss, Todd
Phase II study of Gleevec	Completed; *(Rao et al. Proc ASCO*, 2003; *The Prostate*, 2004)	PDGF immunohistochemistry	21	DiPaola, Goodin
Phase II study of pox PSA vaccine	Completed; *(Kauffman et al. Proc ASCO*, 2002; *JCO*, 2004)	T-cell immunity (ELISPOT)	70	Kaufman, DiPaola
Phase II study of docetaxel	Completed; *(Goodin et al., Proc ASCO*, 2003, *JCO* in Press)	Peripheral blood mononuclear cell bcl-2	25	DiPaola Weiss Goodin
Advanced/Hormone-Refractory Prostate Cancer				
Phase I study of CRA/IFN combined with chemotherapy	Completed; (DiPaola et al., *J Clin Oncol*, 1999)	Bcl-2 in peripheral blood mononuclear cells, PK, P450 evaluation	25	E. White, DiPaola
Phase I study of CRA/IFN combined with weekly paclitaxel	Completed; (Thalasila et al., *Cancer Chemother Pharmacol*, 2003)	Bcl-2 in peripheral blood mononuclear cells	15	E. White, DiPaola Rubin
Phase I study of bcl-2 antisense in HRPC (PI at MSKCC with collaboration for lab correlate)	Completed; (Morris et al., *Clin Cancer Res*, 2002)	Collaboration with main PI at another institution for bcl-2 laboratory studies	20	MSKCC DiPaola (lab component)
Phase I/II study of novel PSA activated peptide-doxorubicin	Completed; (DiPaola et al., *J*	PK of peptide and conjugate	30	DiPaola

conjugate	*Clin Oncol,* **2002**)			
Phase I study of pox PSA/TRICOM vaccine	Completed; *DiPaola et al., Proc AACR, 2004*	T-cell immunity (ELISPOT)	10	DiPaola Lattime
Phase II study of docetaxel and vinorelbine	*Completed: Goodin et al., Proc ASCO,* 2002, *Ca Chem Pharm* 2005 In Press)		40	DiPaola
E3899: A randomized phase II study of CRA/IFN and paclitaxel vs. estramustine, mitoxantrone, and vinorelbine	Completed; *DiPaola et al., Proc ASCO, 2004*	Bcl-2 in peripheral blood mononuclear cells	70 (National)	DiPaola E. White
Phase I and II study of CRA/IFN combined with estramustine and docetaxel (RITE)	Ongoing: *Elsyad et al., Proc ASCO, 2004*	Bcl-2 in peripheral blood mononuclear cells, PK,	10	DiPaola Rubin E. White
Phase I/II study of estramustine in combination with epothilone	Completed; *Wojtowicz et al., Proc ASCO, 2004*	PK	15	DiPaola Rubin
Phase II study of estradiol patch as salvage therapy	Ongoing	Plasma estrogenicity by yeast assay	11	Lambert DiPaola
Phase II study of licorice root derivative combined and docetaxel	Ongoing	Estrogen yeast assays of patient serum		Lambert Gallo DiPaola

Although the focus of the Prostate Program is on investigator-initiated, translational research, CINJ members are also active participants in ECOG and intergroup trials, as well as cooperative efforts with other cancer centers. This work is promulgated by the recent appointment of DiPaola as Chair of the ECOG Genitourinary Committee. In this administrative role, DiPaola is responsible for the development of studies within the committee, as well as serving as principal investigator on a number of studies. Approved and developing studies (in addition to those shown in Table 2) that DiPaola will serve as chair or co-chair include the use of epothilone as a salvage therapy in prostate cancer and a randomized phase III study of Prostvac™ vaccine in combination with GM-CSF in patients with PSA progression after local therapy. The latter is based data from a vaccine trial completed through ECOG demonstrating that the optimal vaccine schedule was a "prime and boost" approach (E7897, Kaufman et al., *JCO* 2004, *Proc. ASCO*, 2002, DiPaola *JCO*, 2004).

DISCUSSION: Program members identified critical determinants of drug sensitivity in human prostate cancer and elucidated novel mechanisms of resistance. These studies informed the development of investigator-initiated clinical trials designed to counter drug-resistance in patients with prostate cancer. The tremendous growth in this area emphasizes the success of this disease-based program in meeting one of the CINJ strategic goals--increasing translational research. However, CINJ also recognized the need for additional strength to complement the leadership of DiPaola. Accordingly, CINJ and the Department of Surgery recruited Ronald Morton, an nationally-recognized urologist who will head the Division of Urology at RWJMS. In addition, CINJ resources were made available to recruit a pathologist to focus on prostate cancer, as well as two medical oncologist to work with DiPaola and Todd. Dr. Mark Stein, medical oncologist was recruited to the GU team in July of 2004. This team of investigators will capitalize on the new mouse model of prostate progression from androgen-dependent to independent disease as preclinical models to investigate new approaches to prevent and/or treat this lethal transition.

3. To improve the control of prostate cancer through early detection, prevention, and information

dissemination.

RATIONALE/CANCER FOCUS: The control of prostate cancer will require more powerful methods of prevention, early detection, treatment, and dissemination of new information to populations at risk. A major thrust of the CINJ Division of Prevention, Control and Population Science (Carcinogenesis and Chemoprevention; Population Science Programs) is to develop effective chemopreventive strategies and apply these to populations at risk. Prostate Program members pursue basic research approaches to understand the molecular mechanism underlying disease initiation. These studies, as well as pre-clinical studies in mutant mice and cell lines will lead to mechanistic based approaches to prevention. The recent recruitment of a cancer epidemiologists who investigate screening and surveillance methods (Lu-Yao), as well as the nutritional basis of hormonally-derived cancers (Bandera) create a new interface with the Population Science Program. Therefore, the work conducted by members of the Prostate Program provides mechanistic basis for new and ongoing cancer control research.

ACCOMPLISHMENTS: The carcinogenic process often involves oxidative and inflammatory processes. For example, Drs. Abate-Shen and Shen recently found that loss-of-function of *Nkx3.1* led to increased oxidative damage to prostatic epithelium as a function of aging. Laskin utilizes rodent models to characterize the effects of oxidation on the bioactivation of carcinogens in the prostate (a tissue with limited cytochrome P540 activity) and how diet effects this process (Laskin et al., *J Toxicol Environ Health A,* 2000; Billack et al., *Biochem Pharmacol,* 2001; Laskin et al., *Adv Exp Med Biol,* 2001; Ahmad et al., *J Leukoc Biol,* 2002; Billack et al., *Am J Physiol Cell Physiol,* 2002). He recently received NCI R01 funding to investigate a previously unrecognized molecular target for preventive agents in the prostate discovered in collaboration with Diane Heck (Carcinogenesis and Chemoprevention). They demonstrated that catalase has dual effects in the prostate including the oxidation of carcinogens to DNA-reactive metabolites (Heck et al., *J Biol Chem,* 2003). They used cDNA clones to generate and characterized cell lines that overexpress catalase activity, an enzyme with high affinity for major genotoxic chemicals that induce prostate tumors when administered to rodents (3,2'-dimethyl-4-aminobiphenyl (DMAB); 2-amino-l-methyl-6-phenyl-imidazo(4,5- b)pyridine (PhIP); N-nitrosobis (2-oxopropyl) amine and; N-methyl-nitrosourea. PhIP is a heterocyclic amine produced during cooking that has only recently been identified as a prostate carcinogen. DMAB, a synthetic aromatic amine, is a member of a large family of aminobiphenyls synthesized by the chemical dye industry. The Laskin group went on to show that several important nutrients, in particular, ferulic acid, vanillic acid and epigallocatechin gallate, are effective and potent inhibitors of the newly discovered role of catalase in the prostate. During the next grant period, collaborative efforts are planned to validate this target in mouse models and in human prostate cancer, identify more potent and selective inhibitors, and initiate clinical trials to assess the development and progression of prostate cancer.

Paul Copeland recently received R01 funding to investigate selenium metabolism and is applying his work to prostate cancer. Dietary supplementation with selenium was reported to decrease total cancer mortality and specifically reduced the incidence of lung, colorectal and prostate cancers (Clark et al., *JAMA,* 1996; Copeland and Driscoll, *Biofactors,* 2001; Copeland and Driscoll, *Methods Enzymol,* 2002; Copeland, *Gene,* 2003). Copeland, a recently recruited authority of selenoproteins, hypothesized that increased dietary selenium is either acting through the production of selenoproteins or through the action of selenium-containing small molecules that have unknown function (Driscoll and Copeland, *Annu Rev Nutr,* 2003). Since many selenoproteins protect against oxidative damage, he is testing the hypothesis that the chemoprotective effect of selenium supplementation is through an increase in selenoprotein expression. He reasoned that if increased dietary selenium is primarily functioning through the selenoprotein pathway, then prostate cancer cells should have altered selenoprotein expression. Indeed, it has been observed that at least one selenoprotein is dramatically reduced in prostate cancer. Dr. Copeland is studying the effects of both increased selenium and increased selenoprotein synthetic capacity on prostate carcinogenesis in model systems. This work will be greatly enhanced through access to the mouse models available to program members. One of the ultimate goals is to identify means by which to modulate the efficiency of selenoprotein synthesis, ideally in a selenoprotein-specific manner.

It is estimated that millions of Americans use nutraceuticals for disease treatment and prevention. Among these numerous unregulated substances are a host of herbal preparations. DiPaola leads a team of investigators interested in the carcinogenic and anticarcinogenic effects of phytoestrogens, with the goal of identifying non-toxic agents for chemoprevention. This work began when DiPaola observed that many of his patients were self-medicating with PC-SPES, a Chinese herbal concoction that was widely used by men to self-medicate their prostate cancer. DiPaola, Hait, Gallo (Carcinogenesis and Chemoprevention) and Lambert described the biological actions and toxic side effects of PC-SPES. They demonstrated the presence of potent phytoestrogens that were a likely biological explanation for both the activity and side effects of this preparation, and emphasized the importance of further study of novel estrogens as active clinical agents in prostate cancer (DiPaola et al., *N Engl J Med,* 1998; Marks et al., *Urology,* 2002). They went on to show that the mixture was contaminated with synthetic substances; this eventually led to the banning of PC-SPES from the market (Marks et al., *Urology,* 2002).

Lambert and DiPaola initiated investigator-initiated clinical trials studying phytoestrogens and pharmaceutical estrogens (DiPaola et al., *N Engl J Med,* 1998; Rafi et al., *Anticancer Res,* 2000; Zhu et al., *J Nat Prod,* 2001; Zhu et al., *Phytochemistry,* 2001; Rafi et al., *J Agric Food Chem,* 2002). They began by testing the safety and efficacy of these substances in men with prostate cancer, with the goal of moving active, non-toxic compounds into prevention trials for men (e.g. African Americans) at high risk. This paradigm follows the successful methods used for tamoxifen in breast cancer. For example, they are studying the activity of licorice root for patients with early disease (NCI-funded project), licorice root combined with taxotere for patients with hormone-refractory prostate cancer (NCI-funded Pilot Project), and an estradiol patch in men with prostate cancer that is refractory to hormonal and chemotherapy (See Tables 2 and 3). In these studies plasma estrogenicity will be determined by a yeast reporter system sensitive to activation of both ER alpha and beta. Further laboratory studies by DiPaola and collaborators identified additional phytoestrogens from licorice root including a novel dihydrophenol (DHP) capable of inducing apoptosis, mitotic arrest, bcl-2 phosphorylation, and microtubule bundling, and filed and received patents for this discovery (Rafi et al., *J Agric Food Chem,* 2002). Recently, the interaction of DHP with AR was studied by computational modeling in collaboration with William Welsh (Cancer Pharmacology/Developmental Therapeutics) (Ai et al., *Chem Res Toxicol,* 2003). These results suggest that DHP could function both as an androgen-receptor antagonist and, unexpectedly, as an estrogen-receptor agonist. Drs DiPaola and Welsh are submitted a NCI grant in October 2004 to further characterize DHP as a lead compound with potentially "ideal" pharmacological characteristics for the prevention or treatment of prostate cancer.

Robert Weiss in collaboration with C.S. Yang (Carcinogenesis and Chemoprevention) (Yang et al., *Annu Rev Pharmacol Toxicol,* 2002; Ju et al., *Nutr Cancer,* 2003; Lambert et al., *J Nutr,* 2003), investigates the effects of green tea constituents in patients with prostate cancer, through clinical trials supported by GPCC Developmental Funds. As part of this trial, concentrations of green tea polyphenols in the prostate are measured following a single dose of green tea administered before prostate surgery.

Members are also beginning to use the mutant mice models described in section 1 (see Table 1) as pre-clinical tools to test chemopreventive agents and to follow these results with studies in the clinic. For example, Abate-Shen and DiPaola are studying the effects of calcitriol (1,alpha 25, dihydroxy-vitamin D3), a vitamin D derivative with antitumor effects *in vitro* and *in vivo*. Proposed mechanisms include the modulation of p21, p27, and the bax/bcl-2 interaction. In clinical studies, calcitriol was shown to slow the rise of PSA in patients with prostate cancer and appeared to enhance the anti-tumor effect of platinum compounds and taxanes. Drs. DiPaola and Abate-Shen initiated a pre-clinical study in *Nkx3.1* mutant mice to examine whether calcitriol can reduce the incidence of prostate cancer in these mice. Preliminary results support the idea that calcitriol prevents the development of high-grade PIN. In parallel, DiPaola is conducting a randomized, trial of calcitriol in men with biopsy-proven high-grade PIN (Table 3). Tissue will be assessed before and after treatment to evaluate the effects of calcitriol in this high-risk population. High-grade PIN is associated with a 40-50 percent

chance of developing prostate cancer. Autopsy series demonstrated that high-grade PIN occurs as early as the fourth decade, and increases in incidence with age. Therefore, non-toxic agents that reduce this intraepithelial neoplasia would be candidates for larger prevention studies.

Table 3. • Investigator-initiated Prevention Trials in Prostate Cancer

TRIAL	STATUS	LABORATORY BASIS AND CORRELATES	N	COLLABORATORS
Phase II study of calcitriol in patients with PIN	Ongoing	Preclinical mouse experiments; transcriptional and translational profiles.	NA	Abate-Shen DiPaola
Assessment of phytoestrogens in PC-SPES in patients with androgen naïve prostate cancer in man and animals	Complete; (DiPaola et al., *N Engl J Med,* 1998; Marks et al., *Urology,* 2002)	Estrogen yeast assays *in vitro* and *in* vivo mouse experiments	8	DiPaola Gallo Lambert
The effect of soy on testosterone and PSA	Complete; (Goodin et al,. Proc ASCO 2004)	Serum LH, Test, PSA	15	Lambert Goodin DiPaola
Phase II study of licorice-root derivative in patients with HNPC.	Ongoing	Estrogen yeast assays of patient serum	16	Lambert Gallo DiPaola
Assessment of Green tea in patients with prostate cancer	Ongoing	Tumor chemistry/apoptotic markers	15	Weiss C.S. Yang

Members strive to develop better methods of early detection and to use screening approaches responsibly and effectively. For example, Weiss collaborates with Armand Sarveysian to investigate the utility of mechanical imaging of the prostate (Perrotti et al., *J Urol,* 1999; Perrotti et al., *Urology,* 1999). They developed a device that detected nodules in prostate phantoms with a sensitivity exceeding that of an experienced urologist. In contrast to digital rectal exam, the results with mechanical examination were independent of the operator's experience. Therefore, the system appears to be a promising means of increasing the accurate and reproducible detection of abnormalities within the prostate (*Urology*, 2001).

The widespread use of PSA testing remains an area of intense investigation. Morton (Muldoon et al., *J Rural Health,* 1996; Witte et al., *Urology,* 1999; Kim et al., *Cancer Res,* 2000; Link and Morton, *Urol Clin North Am,* 2001) received NCI funding to develop a simple, sensitive technique to monitor PSA. This research is based on the fact that PSA testing methods remain both inconvenient and costly when applied to screening. Dr. Morton designed a prototype biosensor chip for quantitating blood PSA levels. This chip is an amperometric immunosensor, which would form the core of an inexpensive handheld device for measuring PSA at the bedside or in the physician's office. A critical goal of this project will be to produce a fusion molecule that shares PSA immunoreactivity and glucose oxidase enzymatic activity. This conjugate molecule will compete with PSA at the chip surface and thereby couple immune recognition to an easily detectable electrical signal. A device of this type should significantly impact the diagnosis and treatment of prostate cancer by lowering the cost and broadening the availability of PSA testing for all patients at risk. This is of particular concern given the striking racial differences in prostate cancer mortality, which may be attributable to inadequate access to PSA screening in medically underserved populations.

Dr. Morton will also collaborate with Grace Lu-Yao, a recently recruited prostate cancer epidemiologist, to study the impact of PSA testing on the practice of urology (Lu-Yao et al., *J Urol,* 1997; Lu-Yao and Yao, *Lancet,* 1997; Lu-Yao et al., *Urology,* 1999; Lu-Yao et al., *Bmj,* 2002; Lu-Yao et al., *J Natl Cancer Inst,* 2003). For example, using cancer registry data and intention-to-treat methodologies, Dr. Lu-Yao showed that prostate-specific 10-year survival for low-grade cancers was similar after prostatectomy, radiotherapy and conservative management, but survival of patients with high-grade cancers was significantly better after prostatectomy. She also examined the rates of radical prostatectomy in Medicare beneficiaries before and after the introduction of PSA testing. The results showed a rapid increase in radical prostatectomies following the introduction of PSA testing followed by a sharp decline seen particularly in older and white men. A third study examined the interval after PSA screening and subsequent risk of incurable prostate cancer. Using men 65 years old or older from nine SEER registries, she found that among those diagnosed with prostate cancer, the risk of non-localized cancer did not differ between those tested two or three years prior to diagnosis and those tested one year prior to diagnosis. However, the rate of prostate biopsy was directly related to the number of PSA tests performed (Yao and Lu-Yao, *J Urol,* 2001). Dr. Lu-Yao used SEER and Medicare data to compare rates of screening, treatment and mortality. These data showed that higher rates of PSA screening, prostate biopsy, radical prostatectomy, and external beam radiotherapy did not affect the adjusted mortality odds ratios in elderly patient populations (Lu-Yao et al., *Bmj,* 2002). In a recent report, Dr. Lu-Yao investigated the use of PSA screening in elderly men (Lu-Yao et al., *J Natl Cancer Inst,* 2003). By using a nationally representative sample of 7889 men who participated in the 2000 National Health Interview Survey, she found that the rate of PSA screening among men aged 75 or older was 32.5%, which was greater than that of fecal occult blood screening among men despite lack of evidence suggesting a benefit in this elderly population.

Lu-Yao also investigates the utility of radical prostatectomies in elderly patients. She used Medicare claims from 1991 to 1994 to identify and quantify the types and risks of complications, re-hospitalization within 90 days, and mortality at 30 and 90 days after perineal or retropubic prostatectomy. On the basis of data from 101,604 men, they found that complications and readmission after prostatectomy are substantially more common than previously recognized, and that older age is associated with elevated surgical mortality and complications (Lu-Yao et al., *Urology,* 1999).

The work of Lu-Yao and Morton will be of critical importance to that of Mrs. Betty Gallo, a leading prostate cancer advocate. An important goal of the Prostate Program is to develop effective strategies for outreach into the community. This has been initiated through involvement of prostate cancer advocates under the tireless leadership of Gallo, who established strong ties with the minority community through the 100 Black Men organization and the Men's Health Network. These efforts include education and screening programs for the African American community, and will provide access to this population for the epidemiological and intervention studies. Ms. Gallo sits on the CINJ protocol review and monitoring committee to ensure the interests of the survivor and advocacy communities are represented.

A major goal of the Gallo Prostate Cancer Center (GPCC) Cancer Control and Education Program is the reduction of prostate cancer incidence, morbidity and mortality among the residents of the State of New Jersey. GPCC focused on cancer control including the education of the public in the State of New Jersey about early detection of prostate cancer, particularly the African community where the need and the risk are both the greatest and the study of novel mechanisms to improve education through understanding aspects of culture diversity. The only available treatments for prostate cancer that are curative require the identification of the disease at these early stages of its development. In order to achieve these goals a pilot project award was given to the 100 Black Men of New Jersey and the Men's Health Network (MHN), Washington, D.C. New Jersey ranks number 1 in per capita incidences of prostate cancer in the United States according to the American Cancer Society, Cancer Facts and Figures, 2003. In 1999 the Gallo Prostate Cancer Center in collaboration with the 100 Black Men of New Jersey, initiated a program to offer free prostate cancer education and screenings to African-Americans in New Jersey. Congressman Donald Payne and Congressman Robert Menendez collaborated with the center to initiate the education and screening program. The program was started in Essex County of New Jersey who has the highest incidence rate of prostate cancer in African-

Americans in the state. The increase of awareness of prostate cancer was achieved through several mechanisms: i. Providing opportunity for more public education and screenings, ii. Preparing and distributing brochures to a variety of community places such as barber shops and churches, iii. Increasing our current outreach efforts to include not only African-Americans but also the male population as a whole. In 1999 there were no educational materials available for the African-American or Latino community about prostate cancer. In our collaboration with the 100 Black Men of New Jersey and the Men's Health Network the center developed culturally sensitive materials for these communities with specific information about that communities incidence rate (brochures attached). These materials were distributed at health fairs, Village Gatherings in underserved population areas, mostly intercity (organized by the 100 Black Men of New Jersey) and prostate cancer education and screening programs as well as distributed to other outreach programs at local hospitals including the Partners and Affiliate Network of the Cancer Institute of New Jersey. The Men's Health Network's primary goal is education and awareness about men's health issues. The program with the MHN has advanced the awareness of prostate cancer on a national and international level.

DISCUSSION: Members identified new mechanism of carcinogen activation, providing new targets for screening and prevention. The also developed new imaging technologies and critically assessed the widespread use of PSA testing. Although the Prostate Program is new, it has already acquired significant expertise in prevention and control research. Promising areas of research include the use of mouse models for discovery of carcinogenic substances, for identifying important new targets for chemoprevention, understanding the function of selenium and selenoproteins, and innovative work on herbal substances. Access to healthy patient populations for preventive trials will be greatly enhanced by the recruitment of Morton, who will expand the Urology service, and the arrival of epidemiologists to take advantage of the strong ties with the African American community. Morton, has considerable experience in the training and dissemination of information to minority communities, thereby providing an even stronger link to the outreach and advocacy work of Gallo.

Future Development

The Prostate Program is built on a strong foundation of laboratory, clinical, and population research. The models developed by program members are all very new; they will be extensively utilized for generating new hypotheses for translational studies. Several examples include the use of calcitriol in mouse models, the work on phytoestrogens, and the targeting of local activation of carcinogens in prostate tissue. The addition of high-resolution small animal imaging studies in collaboration with Jeffrey and Deborah Lasking (Cytokines, Cytokine Signaling, and Cancer) will improve the pre-clinical studies using these mutant programmatic collaborations. The appointment of DiPaola to the ECOG leadership will accelerate translation of many of the concepts developed by Prostate Program members. The ability to leverage CINJ Development Funds created a robust pilot project activity that will bring additional investigators into the field of prostate cancer research. Finally, the arrival of Grace Lu-Yao, Mark Stein and Ronald Morton as well as the recruitment of additional members with expertise in medical and surgical oncology and pathology will help the program build strong relationships with the Prevntion, Control, and Population Science and with the Clinical Science Division of CINJ.

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EDUCATIONAL PROGRAMS FOR RESEARCHERS

As part of the DOE grant award the center established an education program for the basic and clinical researchers. This program included presentations by prostate cancer researchers from UMDNJ and Rutgers University interested in prostate cancer research and invited speakers who are experts in prostate cancer in order to initiate collaborations among prostate cancer researchers.

The GPCC Research Working Groups brought together researchers from the two universities interested in prostate cancer to present their work and encourage collaborations. Presentations were given by UMDNJ and RU prostate cancer researchers. The twenty programs presented can be found in attachment 1.

On October 9, 1999 the center sponsored their first educational workshop entitled "The Disease and the Dilemma" A Workshop on Prostate Cancer". Dr. Leland Chung, Professor of Urology, University of Virginia was the invited speaker. UMDNJ and Rutgers University researchers also presented their research. The program can be found as attachment 2.

The center sponsored a retreat on December 8, 2001 in which 13 investigators participated by presenting their research on prostate cancer. The topics ranged from a discussion of clinical trials to basic studies on prostate development. The program is attachment 3.

A Prostate Cancer Workshop was held on April 24, 2002 as part of the CINJ state-wide cancer retreat in Princeton, New Jersey. Outside lecturers as well as UMDNJ and RU reseachers were invited to share their research findings with the New Jersey researchers. Invited speakers were Dr. Philip Kantoff, Director, The Lank Center for Genitourinary Oncology and Associate Professor of Medicine at Dana-Farber Cancer Institute; Dr. Angel DeMarzo, Assistant Professor of Pathology at John Hopkins Medical Institutions and Dr. Gerald Cunha, Professor of Anatomy and Urology at University of California at San Francisco. The program is attachment 4.

Invited Lecturers:
Norman M. Greenberg, Ph.D.
Scott Department of Urology
Baylor College of Medicine
"TRAMP: A Transgenic Mouse Model for Prostate Cancer Research "
October 18, 2000

Dr. Charles (Snuffy) Myers
Professor of Medicine and Urology at the University of Virginia
"Who is at Risk for Hormone-resistent Disease
May 10, 2002

Simon Cherry, Ph.D.
UCSD
"Technologies for In Vivo Imaging of Mouse Models of Cancer"
December 11, 2003

Attachment 1
GPCC Research Working Group Lectures

November 18, 1999	Dr. Eileen White Prostate Cancer Apoptosis
April 6, 2000	Dr. John Pintar
May 4, 2000	Dr. Longqin Hu "Design of Anticancer Prodrugs for Site-Specific Activation"
June 1, 2000	Dr. K.V. Chin "Analystis of Drug Resistance by cDNA Microarrray and Exo-PKA Activity in Prostate Cancer"
July 6, 2000	Dr. Deidre Nelson "Prostate Cell Apoptosis: Regulators and Effectors"
September 7, 2000	Dr. Arnold Rabson "A Role for NF-kappaB Activation in Prostate Cancer"
October 5, 2000	Dr. Robert DiPaola "Novel Clinical Approaches in Prostate Cancer"
November 2, 2000	Dr. Ramsey Foty "Putting the Squeeze on Cancer" A Novel Approach to the Study of Malignant Invasion"
December 7, 2000	Dr. Stuart Lutzker Cell-cycle Check Pints in Prostate Cancer Cells"
January 4, 2001	Dr. Longhua Li "Understanding Tumor Suppressor Gene Involvement during Breast Cancer Development on a Genome-Scale"
February 1, 2001	Dr. Jeffrey Laskin "Mechanisms in Photochemotherapy"
March 1, 2001	Dr. Robert Weiss "Mechanical Imaging of Prostate: A Novel Means of Prostate Examination
April 5, 2001	Dr. Keith Bupp "Use of Random Display Envelope Libraries to Target Retroviruses to Specific Cell Types"

Attachment 1 continued

October 4, 2001	Dr. Robert DiPaola "Targeting Apoptosis in Prostate Cancer"
November 1, 2001	Dr. Deidre Nelson "Differential Short Versus Long-term Protection of Transformed Rate Prostate Cells to Chemotherapeutic Drug-Induced Apoptosis by Bcl-2 and Eib 19K"
December 6, 2001	Dr. Robert Weiss "The Role of Green Tea in Prostate Cancer
January 3, 2002	Dr. Lonqin Hu "Design of Anticancer Prodrugs for Site-Specific Activation"
March 7, 2002	Dr. John Pintar "Genetic Studies of IGFBP Deficient Mice"
April 4, 2002	Dr. Stuart Lutzker "The Mitotic Checkpoint and Senstivity of Proostate Cancer Cells to Antimicrotubule Drugs"
May 2, 2002	Dr. C.S. Yang "Nutrition and Prostate Cancer"

Attachment 2
The Disease and the Dilemma: A Workshop on Prostate Cancer
October 9, 1999

9:00	Welcoming Remarks Dr. William N. Hait Dr. Steven Ward
9:30	Keynote Address Dr. Leland Chung Professor of Urology University of Virginia
10:45	Prostate Development and Its Relationship to Carcinoma Dr. Michael M. Shen
11:30	Molecular Biology of the Normal and Abnormal Prostate Dr. Cory Abate-Shen
12:15	Hormonal Mechanisms of Prostate Carcinogenesis Dr. Michael A. Gallo
1:00	Lunch
2:00	Prostate Cancer: A Urologist Perspective Dr. Kenneth Cummings
2:45	Clinical Approaches to Treating Prostate Cancer Dr. Robert DiPaola
3:30	Closing Remarks

Attachment 3
GPCC Scientific Retreat
December 8, 2001

8:30	Dr. Cory Abate-Shen	Introduction
8:35	Dr. Robert DiPaola	Translational Research in Prostate Cancer
8:50	Dr. Parvesh Kumar	A Novel Therapeutic Strategy Testing the Safety and Feasibility of Concurrent Docetaxel and 3-D Conformal Radiation Therapy in patients with High-Risk Locaized Adenocarcinoma of the Prostate: Progress Report of an On-going Phase I/II Trial
9:05	Dr. Tamara Minko	Enhancing the Efficacy of Chemotherapeutic Drug by the Suppresssion of Antipoptotic Cellular Defense
9:20	Dr. Steve Marcella	PSA Screening and Prostate Cancer Mortality: Preliminary Evidence of Increased Incidence of Prostatism in Clinically Aggressive Prostate Cancer
9:35	Dr. Carlos Molina	Regulation of the Transcriptional Repressor Inducible cAMP Early Repressor in Prostate Cancer Cells
9:50	Dr. Keith Bupp	Targeting Retrovirus Using random Display Envelope Libraries
10:05	Dr. Stuart Lutzker	Abrogation of the Mitotic Spindle-checkpoint in Prostate Cancer Cells and Sensitivity to Antimicrotubule Drugs
10:20	Dr. John Pintar	Searching for Prostate Abnormalities in IGFBP KO Mice
10:35	Dr. Arnold Rabson	Mechanisms of Consitutive NF-kB Activation in Human Prostate Cancer Cells
10:50	Dr. William Hait	Molecular Determinants of Response to Therapy in Patients with Prostate Cancer

Attachment 3 continued

11:05	Dr. Zui Pan	Ca2+ Signaling and Bax Translocation in Apoptosis of Prostate Cancer Cell Lines
11:20	Dr. Michael Shen	Molecular Determinants of Response to Therapy in Patients with Prostate Cancer
11:35	Dr. Cory Abate-Shen	Cooperativity of Tissue-Specific and Broad-Spectrum Tumor Suppressor Genes in a Mouse Model of Prostate Cancer

Attachment 4
The Dean and Betty Gallo Prostate Cancer Center Symposium
April 24, 2002

Chairs: Drs. Cory Abate-Shen and Dr. Robert DiPaola

2:00	Dr. Gerald Cunha	Tissue Recombinant Models of Prostateic Carcinogeneis
2:40	Dr. M. Kim	Use Models of Prostate Cancer Initiation and Progression
3:00	Dr. Philip Kantoff	Clinical Progress in Prostate Cancer
3:40	Dr. K. Rao	Characterization of a Novel Prostate Specific Antigen Activated Peptide Doxorubicin Conjugate in Patients with Prostate Cancer
4:00	Dr. Angelo DeMarzo	Prostate Cancer: Precursors and Pathobiology
4:40	Dr. Deidre Nelson	Differential Short- Verus Long-Term Protection by BCL-2 and E1B19K on Transformed Rate Prostate Cells to Chemotherapeutic Drug-Induced Apoptosis
5:00	Dr. M. Fredericks	The MAPK Pathway Directs the Proteasomal Degredation of Inducible CAMP Early Repressor During the Cell Cycle of Prostate Cancer Cells
5:20	Dr. Junghan Suh	Mechanisms of Constitutive NF-kB Activation in Human Prostate Cancer Cells

Co-Leaders: Cory Abate-Shen, Ph.D.
Robert S. DiPaola, M.D.

Dr. Cory Abate-Shen Publications:

Bhatia-Guar, R. Donjacour, A.A., Sciavolino, P.J., Kim, M., Desai, N., Young, P., Norton, C., Gridley, T., Cardiff, R.D., Cunha, G.R., Abate-Shen, C. and Shen, M.M. (1999). Roles for *Nkx3.1* in prostate development and cancer. *Genes Dev.* 13:966-977.

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Abate-Shen, C., Kim, M., Desai, N., Banach-Petrosky, W., Cardiff, R. and Shen, M.M. (2002). Mouse models of prostate cancer initiation and progression. American Association for Cancer Research, Annual Meeting, San Francisco, CA.

Abate-Shen, C., Kim, M., Ouyang, X., Gao, H., Banach-Petrosky, W., Sun, X., Cardiff, R. and Shen, M.M. (2002). Mouse models of prostate cancer initiation and progression. Cold Spring Harbor Meeting on Mouse Molecular Genetics, Cold Spring Harbor, NY.

Dr. Cory Abate Shen Presentations:

1999 US-Japan Program Workshop on Developmental Regulators and Cancer, Maui HI

NIH, Departments of Urology and Pathology, Bethesda MD

Distinguished Lecture Series, Wistar Institute, PA

U.C. Davis Cancer Center Seminar Series, Davis, CA

2000 American Association for Cancer Research Special Conference, Transcription Factor Pathogenesis of Cancer at the Millennium, Dana Point CA

Jonsson Cancer Comprehensive Center, Prostate Cancer Seminar Series, University of California, Los Angeles CA

MD Anderson Cancer Center, University of Texas, Houston TX

Max Delbruck Center for Molecular Medicine, Berlin, Germany

German Cancer Research Center, Heidelberg, Germany

Mouse Models of Human Cancer Consortium, Chantilly, VA

SPORE grant program Annual Meeting, Chantilly, VA

Pre-clinical Models in Prostate Cancer Research, Houston, TX

2001 Symposium Organizer, Annual Meeting of the American Association for Cancer Research, New Orleans, LA

NCI/Mouse Models of Human Cancer Consortium Satellite Meeting on PreClinical Trials, Bethesda MD

Skirball Institute, New York University, New York, NY

MD Anderson Cancer Center, University of Texas, Houston, TX

Mouse Models of Human Cancer Consortium Steering Committee Meeting, San Francisco, CA

UCSF Mini-Symposium on Mouse Models of Angiogenesis, San Francisco, CA

Meeting Organizer, Mouse Models of Prostate Cancer, Bar Harbor, MI

2002 Huntsman Cancer Institute at the University of Utah, Salt Lake City, Utah

Mouse Models of Human Cancer Consortium Steering Committee Meeting, Boston, MA

Chair and Invited Speaker, Cold Spring Harbor Meeting on Mouse Molecular Genetics, Cold Spring Harbor, NY

9th Prouts Neck Meeting on Prostate Cancer, Prouts Neck, ME

First Joint Meeting of the Mouse Models of Human Cancers Consortium (MMHCC) and the Prostate SPOREs, Bethesda, MD

Dr. Robert S. DiPaola Publications:

DiPaola R.S., Aisner J. Overcoming bcl-2 and p53 mediated resistance in Prostate Cancer. Seminars of Oncology, 26: 112-116, 1999.

DiPaola R.S., Rafi M., Vyas V., Gupta E., Toppmeyer D., Rubin Eric, Patel G., Goodin S., Medina P., Zamek R., Zhang C., White E., Hait W.N. Phase I clinical and pharmacologic study of 13-cis retinoic acid, alpha interferon and paclitaxel in patients with prostate cancer and other advanced malignancies. J Clin Oncol 17:2213-2218, 1999.

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Eid J.E., Brunner M., Segal L., Cummings K.B., Weiss R.E., Goodin S., Todd M., Aisner J., DiPaola R.S. Effect of P-30 Protein and Tamoxifen on TGF-Beta1 and IGF-1 in Patients with Prostate Cancer, Urologic Oncology 6:243-247, 2001.

DiPaola RS, Chenven ES, Shih WJ, Lin Y, Amenta P, Goodin S, Shumate A, Rafi MM, Capanna T, Cardiella M, Cummings KB, Aisner J., Todd M. Mitoxantrone in patients with prostate specific antigen progression after local therapy for prostate cancer. Cancer. 2001 Oct 15;92(8):2065-71.

DiPaola R.S., Patel J., Rafi M.M. Targeting Apoptosis in Prostate Cancer. Hematology/Oncology Clinics of North America. 15:3:509-524, 2001.

Rafi MM, Vastano BC, Ho C-T, Ghai G, Rosen RT, and DiPaola RS. Novel polyphenol molecule isolated from licorice root (glycrrhiza glabra) induces apoptosis, G2/M cell cycle arrest, and bcl-2 phosphorylation in tumor cell lines. J. Agric and Food Chemistry 50:677-684, 2002.

DiPaola RS, Rinehart J, Nemunaiti J, Effinghaus S, Rubin E, Capanna T, Ciardella M, Fontaine M, Adams N, Williams A, Schwartz M, Winchell G, Wickersham K, Deutsch P, Yao S. Characterization of a novel prostate specific antigen activated peptide-doxorubicin conjugate in patients with prostate cancer. J Clin Oncol. 2002 Apr 1;20(7):1874-1879.

S. Goodin, K. Rao, and R.S. DiPaola. State of the Art Therapies in Prostate Cancer. Oncologist 360-70, 2002.

DiPaola RS. To Arrest or not G2-M cell cycle arrest. The Biology Behind. Clin Cancer Res, 3311-4, 2002.

Thalasila, A., Poplin, E., Shih, J., Dvorzhinski, D., Capanna, T., Doyle-Lindrud, S., Beers, S., Goodin, S., Rubin, E., and DiPaola, R. S. A phase I trial of weekly paclitaxel, 13- cis-retinoic acid, and interferon alpha in patients with prostate cancer and other advanced malignancies. Cancer Chemother Pharmacol, *52*: 119-124, 2003.

DiPaola, R. Durivage, H. and Kamen, B. High time for low-dose prospective clinical trials. Cancer, 98: 1559-1561, 2003.

Yao, S. L. and DiPaola, R. S. An evidence-based approach to prostate cancer follow-up. Semin Oncol, 30: 390-400, 2003.

Dmitri. Dvorzhinski, Anu. Thalasila, Paul. Thomas, Diedra. Nelson, Hong Li, Eileen. White, Robert S. DiPaola. A novel proteomic co-culture model of prostate cancer cell growth. Proteomics. 4:3268-3275, 2004.

Dr. Robert S. DiPaola Presentations:

1999

NOVEL THERAPIES IN CANCER OF THE PROSTATE:TARGETING BCL-2, Cancer Center Grand Rounds, University of Pennsylvania, Philadelphia PA, 1/99.

NOVEL THERAPY FOR PROSTATE CANCER, Seminar, University of Oklahoma, 2/99.

MODULATION OF PACLITAXEL CHEMOTHERAPY, Combined Medical and Radiation Oncology Grand Rounds, New York University, 3/17/99.

A UNIQUE PERSPECTIVE IN THE TREATMENT OF PATIENTS WITH HORMONE SENSITIVE PROSTATE CANCER, Univ of Chicago, taxotere seminar,4/27/99

PROSTATE CANCER, Grand Rounds, St.Vincent's Hospital, Staten Island, 5/6/99

NOVEL THERAPIES FOR PROSTATE CANCER, Oncology Grand Rounds, St. Elizabeth Hospital. NJ, 5/13/99

WEEKLY TAXOL/RETINOID/INTERFERON IN PROSTATE CANCER, MD Anderson W.I.S.E. conference, NY Palace Hotel, NY, 12/18/1999

2000

TAXOL/RETINOID/INTERFERON FOR HORMONE REFRACTORY PROSTATE CANCER, Fox Chase Investigators Meeting, Mandalay Bay, Lanai, 3/16/2000

THE ROLE OF CHEMOTHERAPY FOR PROSTATE CANCER, BMS Symposia, Las Vegas, 3/2000

ASCO UPDATE ON PROSTATE CANCER, BMS Symposia, Las Vegas Nevada, 6/30/2000

NOVEL THERAPY IN PROSTATE CANCER, Medical Oncology Symposia, Seattle WA. 8/10/2000

RETINOID, INTERFERON AND TAXOL RANDOMIZED AGAINST ESTRAMUSTINE, NAVELBINE, AND MITOXANTRONE, Glaxo Advisory Board, Denver CO, 8/25/2000

OVERVIEW OF PROSTATE CANCER, Distinguished lecture, Brookdale Medical Center, NY, 9/6/2000

AVENTIS ADVISORY BOARD MEETING, Lake Tahoe Nevada, 9//19/2000

NOVEL ESTROGENS IN PROSTATE CANCER, CAPCURE SYMPOSIA, Lake Tahoe Nevada, 9/24/2000

PROSTATE CANCER OVERVIEW, Medical Oncology Symposia, Intercontinental Hotel, Chicago, 10/6/2000

PC-SPES IN PROSTATE CANCER, THE AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO) SPECIAL SESSION LECTURE, Boston MA,10/23/2000

2001

UPDATE ON THERAPY FOR HRPC, Aventis advisory board, NY NY, 3/8/2001

AACR SESSION: PROSTATE CANCER OF MICE AND MEN: Chairman, New Orleans, LO 3/25/2001

TRANSLATIONAL APPROACHES IN PROSTATE CANCER, Oncology Grand Rounds at Dana Farber, Boston MA, 4/19/2001

A PSA ACTIVATED PRODRUG IN HRPC, MERCK ADVISORY BOARD, San Fran, CA, 5/11/2001

EFFECT OF ESTROGENS IN PROSTATE CANCER, Symposia on Genes and the Environment, NATIONAL ACADEMY OF SCIENCES, Washington DC, 5/17/2001

PC-SPES and prostate cancer, NATIONAL PROSTATE SYMPOSIA (NMCR): WASHINGTON DC, 5/26/2001

Treatment for stage D2 prostate cancer, NATIONAL PROSTATE SYMPOSIA (NMCR): Marriott Eastside NY, NY, 7/28/2001

Chairman of session and lecture on Estrogens and Prostate cancer, GORDON CONFERENCE, NH, 7/8/2001

State of the art treatment of hormone refractory prostate cancer, MAYO CLINIC SYMPOSIA, Amelia Island, FL 8/16/2001

Treatment for stage D2 prostate cancer, NATIONAL PROSTATE SYMPOSIA (NMCR): CHICAGO, 8/25/2001

Phytoestrogens in prostate cancer, CAPCURE Lecture, Lake Tahoe, 9/9/2001.

Lecture "Hormone refractory prostate cancer", NMCR Prostate Symposia, Dallas TX, 9/292001

Lecture on chemotherapy in prostate cancer. NMCR prostate symposia, Vegas, 11/3/2001

AMERICAN SOCIETY OF RADIATION ONCOLOGY (ASTRO), Special lecture. Complimentary medicine in Prostate cancer, 11/6/2001.

2002

NOCR SYMPOSIA ON PROSTATE CANCER, Atlanta Georgia, 2/12/2002.

ONCOLOGY SYMPOSIA ON BLADDER AND PROSTATE CANCER, Las Vegas NV, 2/24/2002

CYTOTOXIC CHEMOTHERAPY IN HRPC, Biltmore, Miami, 3/23/2002.

NOVEL APPROACHES IN PROSTATE CANCER: Medical Grand Rounds at Graduate Hospital, Philadelphia, 5/8/2002.

Presentation on PSA VACCINIA/FOWLPOX VACCINE WITH AND WITHOUT G-CSF FOR PATIENTS WITHS STAGE D0 PROSTATE CANCER (ECOG 5800) at Therion Advisory Board meeting, Orlando FL, 5/17/2002.

NMCR SYMPOSIA ON PROSTATE CANCER, NY, NY, 6/14/02

ASCO HIGHLIGHTS IN GU ONCOLOGY, San Diego CA, 6/30/02

CYTOTOXIC THERAPY IN PROSTATE CANCER, IPCME, St Petersburg FL, 7/12/02

PROSTATE SYMPOSIA, NMCR, Inverness CO, 7/26/02

NCI PSA VACCINE WORKING GROUP, Bethesda MD, 7/19

NCI WORKING GROUP ON RESEARCH WITH PC-SPES, Bethesda MD, 8/12/02

2003

AVENTIS ADVISORY BOARD, Prostate Cancer and Bcl-2, 1/03

MONTEFIORE SYMPOSIA LECTURE ON PROSTATE CANCER, NY, 6/03

TRANSLATIONAL RESEARCH IN PROSTATE CANCER: Jefferson Medical Center, Urology distinguished Lecture 2/03.

PROSTATE CANCER THERAPY: July, 18, 2003, Invited Speaker,. "ASCO highlights" Network for Medical Communication and Research, Las Vegas, NV.

December 18, 2003, Invited Speaker, "Amonafide Investigators Meeting", Chicago, IL.

OVERVIEW OF THERAPY FOR GU CANCER AT ASCO 2003. July 26, 2003, Invited Speaker, "ASCO highlights" Network for Medical Communication and Research, Hyatt Regency La Jolla, San Diego, CA.

ASCO 2003. August 9, 2003, Invited Speaker, "ASCO highlights Genitourinary Malignancy"Network for Medical Communication and Research, New York, NY.

August 25, 2003, Invited Speaker by NCI "Prostate Vaccine Program" Marriott Pookshill, Bethesda, Maryland.

September 19-20 2003, Invited Speaker, "Challenging Cases in Prostate Cancer"Network for Medical Communication and Research, Chicago, IL.

September 25, 2003 Grand Rounds, Invited Speaker, "High Risk prostate Cancer", Stony Brook University Hospital, Stonybrook NY.

October 3, 2003 Invited Speaker, MSKCC "ECOG Prostate Debate" – New York Westin Hotel, New York, NY.

October 4, 2003, Invited Speaker, "CTEP's studies of PROSTVAC and PANVAC", Therion Biologic, The Crowne Plaza Hotel, Times

2004

February 19-20, 2004, Invited Speaker "Genitourinary Cancer" 10th Annual Meeting, NMCR Educational Symposia, Las Vegas, NV.

FUTURE OF SYSTEMIC THERAPY IN PROSTATE CANCER: ASCO 2004 EDUCATIONAL SESSION, New Orleans.

July 2004. American College of Surgeons (ACOSOG), GU session "ECOG GU trials agenda", Chicago.

June 22-23, 2004, Invited Speaker, "ASCO review" - Columbus Community Clinical Oncology Program, Columbus, Ohio.

TRANSLATIONAL GU SYMPOSIA "GENITOURINARY MALIGNANCIES:BENCH, BEDSIDE, AND COOPERATIVE GROUPS" June 24-25, 2004, Invited Speaker, The University of Iowa College of Medicine, Iowa City, IA.

September 18, 2004. Invited Speaker, Future of Prostate Cancer: Urology/Medical oncology symposia on developing plans to increase Cooperative Group trial accrual. Four Seasons, Chicago.