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In This Issue

Einhorn Honored for Career in Cancer Research

Indiana University Cancer Center oncologist **Lawrence Einhorn, MD** (Experimental Therapeutics and Behavioral Oncology and Cancer Prevention Program member), has been honored for his contributions to the field of cancer research by the American Society of Clinical Oncology.

Dr. Einhorn was awarded the Distinguished Service Award for Scientific Achievement at the group's annual meeting earlier this month. The award is presented annually to an oncologist who has significantly contributed to the field of cancer research.

Dr. Einhorn, who is a Distinguished Professor at IU and a professor of medicine at the Indiana University School of Medicine, has spent his career looking for better treatments for cancer patients. He is a recognized authority on the treatment of urologic and lung cancer and certain other tumors, but is perhaps best known for his work in the field of testicular cancer.

In 1974, he and IU urologist John Donohue, M.D., developed a chemotherapy regimen and surgical technique for testicular cancer patients. Their research changed a disease that was frequently a death sentence to a disease with a 95 percent cure rate.

Dr. Einhorn has been on the testicular cancer world stage since his best-known patient Lance Armstrong was successfully treated in 1996 by a team of specialists at the IU Cancer Center. Armstrong has since won five Tour de France championships and is about to embark on his sixth race.

Part of the now-standard regimen developed by Dr. Einhorn for testicular cancer included a relatively new platinum-based drug. Today, platinum-based chemotherapy regimens are used widely in treatment many different forms of cancer including ovarian, bladder and lung.

A former president of ASCO, Dr. Einhorn was honored by the organization in 1990 with its prestigious Karnofsky Memorial Award. ASCO is the leading professional organization representing physicians who treat people with cancer. With more than 21,500 members from more than 100 countries, ASCO's members set the standard for patient care worldwide.

Dr. Einhorn has been recognized with several prestigious awards as a result of his work as a clinician researcher including the Richard and Hinda Rosenthal Foundation Award for Cancer Research, presented in 1981 by the American Association of Cancer Research; the 1983 American Cancer Society Medal of Honor; and the 1992 Kettering Prize for Cancer Research, awarded by the General Motors Foundation. In 2001, he was elected to membership in the National Academy of Sciences.

A native of Dayton, Ohio, Dr. Einhorn received a bachelor's degree from IU and a medical degree from the University of Iowa. He completed his internship and residency at the IU School of Medicine and hematology/oncology fellowships at IU School of Medicine and the M.D. Anderson Hospital and Tumor Institute in Houston, Texas. He joined the IU School of Medicine faculty in 1973 and was named a distinguished professor at the university in 1987.

Loehrer Receives Exemplary Service Award from Foundation for Thymic Cancer Research

Patrick Loehrer, Sr., MD, Associate Director for Clinical Research at the IU Cancer Center, received the first "Exemplary Service Award" from the Foundation for Thymic Cancer Research at a fundraiser in April in Atlantic City. This award was given to Dr. Loehrer, on behalf of all the thymic cancer patients to whom he has given help and hope, as a symbol of their gratitude.

Dr. Loehrer is an internationally-known expert in the diagnosis and treatment of thymoma, a benign condition of the thymus, and thymic carcinoma. He has been the principal investigator on numerous trials and is widely published on the subject. Under Dr. Loehrer's direction, the Indiana University Cancer Center has developed considerable expertise in thymoma and thymic malignancies, providing services to patients and physicians worldwide. The "Exemplary Service Award" honors the exceptional service that Dr. Loehrer provides by concentrating his research and clinical efforts on thymic carcinoma, a rare disease representing about .2-1.5% of all malignancies.

"Dr. Loehrer has been a beacon of hope to us all," states Alan Niebauer, co-founder of the Foundation for Thymic Cancer Research whose wife Barbara is a thymic cancer survivor.

Among other accomplishments, Dr. Loehrer has been a professor of Indiana University School of Medicine since 1983 and has been named the Kenneth Wiseman Professor of Medicine. He is also co-founder of the Hoosier Oncology Group, an innovative program that encourages community physicians in eight different states to conduct clinical trials.

The Foundation for Thymic Cancer Research is dedicated to helping patients with all thymic-related cancers by collecting and sharing information and patient histories, promoting research, developing support systems and improved understanding, and creating a database of health professionals with thymic cancer expertise.

Photo Left: Dr. Pat Loehrer (middle left), Exemplary Service Award recipient of the Foundation for Thymic Cancer Research, is pictured here with Barbara Neibauer (middle right), a thymic cancer survivor, and her husband Alan (far left). The Neibauers are co-founders of the foundation and the Atlantic City fundraiser. Mary Lynn Rampmeyer, pictured far right, is also fighting the disease and is a patient of Dr. Loehrer.

Champion Receives ACS Grant to Study Quality of Life in Younger Breast Cancer Survivors

Victoria Champion, DNS, Associate Director for Cancer Prevention and Control at the IU Cancer Center, was awarded a $1.8 million grant from the American Cancer Society (ACS) to study how quality of life among younger and older breast cancer survivors contrasts.

The study will compare the differences in quality of life of women cancer survivors ages 45 and younger, with women ages 55 to 70. Differences will be evaluated through a comprehensive assessment of physical, psychological, social, and spiritual variables.

Led by Champion, distinguished professor in the Department of Environments for Health at Indiana University School of Nursing, the study will involve investigators from both Indiana University and Northwestern University. **Brian Giesler, PhD and Joan Haase, PhD** from the Indiana University School of Nursing, **George Sledge, MD and Stephen Williams, MD** from the Indiana University School of Medicine, and **Fred Unverzagt, MD** from the Department of Psychiatry will be participating.

Researchers will assess how survivors' spouses or significant others adjust to living with a cancer survivor. They will also examine how breast cancer survivors might have reorganized priorities upon receiving a new lease on life.

Data will be examined after the third year to develop and pilot an intervention study based on previous results. Identified long-term adverse effects of disease and treatment on breast cancer survivors who are age 45 and under at diagnosis will lead to proactive treatment and counseling for patients and, ultimately, better quality of life.

The five-year grant will support the first study from ACS to compare the unique effects of quality of life for younger women and their partners.

"We want to see how these younger survivors have been uniquely affected by the diagnosis, treatment, and remission of cancer," Champion said. "Younger women are usually pre-menopausal, which can increase the rate of cancer growth. They also can be thrown into menopause because of treatment, which affects the quality of their sexual relationships."

Furthermore, Champion said, younger women can experience side effects from chemotherapy such as numbness, weight gain and fatigue, which may affect their overall quality of life.

Champion, who is recognized internationally for creating tailored interventions for women, is associate dean for research at IUSON, scientific director of the Mary Margaret Walther Program for Cancer Care Research and associate director of cancer control for the Indiana University Cancer Center. Since 1984, her research in early detection, cancer survivorship and quality of life has been funded by the National Institutes for Health.

Scientific Abstract

Breast cancer occurs in a significant number of young women. Approximately 9% of breast cancers occur before age 45. The survival rate for women younger than 45 is 89%, thus a significant number of young breast cancer survivors exists. Little or no research has examined the differential impact of breast cancer in younger women. The primary purpose of this study is to compare breast cancer survivors who were age 45 or younger at diagnosis with a group of survivors who were 55 to 70 at diagnosis. Additionally they will be matched with an acquaintance control group of well females (age matched to younger group) on the quality of life variables of physical functioning, psychological

functioning, social functioning, and spiritual functioning. Type of surgery and presence or absence of hormonal therapy and time since diagnosis will be used as covariates. A second aim is to compare the male partners of younger breast cancer survivors with male partners of the older survivors and controls on the same quality of life variables. Champion and colleagues will explore the relationships between quality of life variables (physical functioning, psychological functioning, social functioning, and spiritual functioning) mediating variables (self efficacy, perceived control, and social support) and antecedent variables (demographics, disease, and treatment). Additionally investigators will explore the impact of partner QOL variables on survivors QOL. All participants must be 18 years of age or older and continuously disease free for three years after initiation of treatment. Eligible women will have participated in ECOG trials that extended from 1993 to 1998. Controls will be matched for age within 5 years, education, and race. A cross-sectional research design will use mailed survey, telephone survey, and medical record data to obtain information. Survey data will be collected using computer assisted telephone interviews by highly trained female interviewers.

All variables will be measured with instruments that have been tested for reliability and validity. Power calculations indicate an adequate sample size. Regression and Anova models will be used for primary comparison between breast cancer survivors groups and younger breast cancer survivors and controls. Partners will be compared with parallel analyses. Regression models will be used to assess relationships between antecedent, mediating, and outcome variables. By identifying long-term adverse effects of disease and treatment on breast cancer survivors who are age 45 and under at diagnosis, we will be better able to proactively treat and counsel patients to promote better quality of life.

Kelley Receives NCI Grant to Study Mechanism for Enhancing Ovarian Tumor Sensitivity

Mark Kelley, PhD (Experimental Therapeutics Program co-leader) received a grant from the National Cancer Institute for the project entitled, "Imbalancing DNA BER to Enhance Ovarian Tumor Sensitivity." If successful, investigators believe these studies will create very effective reagents in a therapeutic gene therapy setting in the clinic for ovarian and other cancers.

The overall significance of this project relates to the ability to imbalance the DNA base excision repair (BER) pathway in ovarian tumor cells, increasing their sensitivity to chemotherapeutic and ionizing radiation (IR) agents. Kelley and colleagues will attempt to accomplish this goal using mutants of the human apurinic/apyrimidinic endonuclease (APE1) enzyme, overexpression of N-methylpurine DNA glycosylase (MPG), both targeted to the nucleus and mitochondria, as well as small (short) interfering RNA (siRNA) for APE1. Investigators will also utilize tumor specific promoter expression in both cell lines and an animal model to develop the usefulness of this approach. Preliminary data indicates that some constructs are effective, and now by combining APE1 mutants and MPG, Kelley and colleagues might further enhance tumor cell sensitivity.

Karen Pollok, PhD (Experimental Therapeutic Program Member) is co-PI and **Constantin Yiannoutsos, PhD** (Biostatistics and Database Management Core Director) is co-investigator for the project.

Scientific Abstract

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NOD/SCID mice. If successful, Kelley and colleagues believe these studies will create very effective reagents in a therapeutic gene transfer/therapy setting in the clinic, as well as shed light on the role of both nuclear and mitochondrial BER in cancer cells.

Langer Receives Phase II Small Business Technology Transfer Award for Radiotherapy

Mark Langer, MD, Experimental Therapeutics Program member and a physician in the Department of Radiation Oncology, is principal investigator on a phase II Small Business Technology Transfer Grant award entitled "Method to Guarantee the Quality of Radiotherapy Plans." A successful project result should allow modern radiotherapy technology to be extended to more patients, offer better assurance of reliability, and extend greater control to physicians and patients in the design of individual treatments.

The research work blends applied mathematics and operations research with emerging issues in medical physics and clinical radiotherapy. The purpose of this research is to develop and engineer algorithms or interfaces that can better direct the assembly of radiotherapy treatment from the huge number of components available to the planner operating with new technologies such as IMRT. IMRT, or intensity modulated radiotherapy, breaks down traditional beams into hundreds of smaller components, each of which can be individually manipulated, but there is no efficient way to discover how the elements should be combined.

This research will integrate planning and delivery constraints to show how the beams and their individual components should be arranged to respect physician prescribed limits, raise tumor dose to as high levels as possible, and exhibit the choices available.

Lech Papiez, chief of medical physics in the department is a collaborator. The applicant small business organization is Advanced Process Combinatorics of West Lafayette and the collaborative research institution is Indiana University School of Medicine; Purdue University is a major subcontractor contributing faculty and students from its schools of Industrial and Chemical engineering.

Scientific Abstract

This project will develop a package of planning products for radiation treatment that will introduce a measure of quality assurance now lacking, provide clinicians the opportunity to raise tumor dose, and expose the tradeoffs among the treatment constraints and objectives. The new approach based on mixed integer programming (MIP) will insist that that the dose distributions prepared for patients do not fail to meet the conditions specified because of inferior performance in a planning routine. The result will be a package for picking beams and beam angles, constructing intensity profiles, and evaluating the effect of uncertainties in treatment objectives or in target and organ positions. Constraints can include dose, dose-volume, and homogeneity limits, and restrictions on beam number. Phase I demonstrated the feasibility of using MIP to optimize tumor dose to within a known error of the best possible while enforcing prescribed constraints, and revealed the tradeoffs among the objective and constraints. Phase II aims to speed performance by customizing a proprietary solver to the developed algorithms and adding new formulations, to integrate the processes of intensity optimization and treatment delivery in order to limit the dose distortions users now face, and to engineer displays of the multidimensional tradeoffs present.

Matei Receives Clarian Values Grant to Study Ovarian Cancer Marker PDGF

Daniela Matei, MD (Experimental Therapeutics Program member) received a Clarian Values Grant for the project entitled "Markers of Sensitivity to PDGFR Inhibition in Ovarian Carcinoma In-Vivo". The major goal of this project is to advance understanding of the PDGF-regulated growth pathway in ovarian carcinoma.

This is a novel area of research that has evolved from the Matei's work in the laboratory. This project is linked directly to a clinical protocol that proposes to test the efficacy and safety of imatinib mesylate in combination with docetaxel for patients with advanced ovarian cancer. The experiments outlined in this proposal will investigate markers of activation of the PDGFR pathway in clinical specimens and their impact on sensitivity to treatment. Matei and colleagues will also investigate PI3K/Akt-dependent mechanisms responsible for the effects of treatment with imatinib and docetaxel in-vitro.

At the completion of this project, investigators expect to identify in clinical specimens critical elements engaged by PDGFR activation. They expect to conclusively determine whether Akt activation impacts response to treatment targeting PDGFR in-vivo. Data from the clinic will be taken back to the laboratory, and used as preliminary data for a project aimed at investigating the functional role of PDGFR in ovarian carcinoma.

This research has direct clinical applications and could lead to the development of novel therapeutic interventions for patients with ovarian cancer. Patients with recurrent ovarian cancer have few therapeutic options. Chemotherapy offers limited and temporary benefit. Finding novel therapeutic interventions has the potential of improving the quality of life and survival of these women. Dissecting out the complex signaling network altered by PDGFR inhibition, as proposed in this project, will identify molecular markers that could be used for selecting patients with heightened sensitivity to PDGFR inhibition in the future. This proposal will advance knowledge in the field of ovarian cancer translational research.

Clarian Health Values grants are awarded to projects that support any of the seven values of this Indianapolis-based hospital system. Matei's project will directly support two values – excellence in research and devotion to quality of patient care.

Scientific Abstract

The central hypothesis for this proposal is that engagement of the PDGF –PDGFR signaling pathway is essential for ovarian tumor growth and survival. Thus, specific inhibition of this axis could lead to potential significant therapeutic interventions for patients with ovarian cancer. Data generated in Matei's laboratory support the fact that PDGFR inhibition by receptor tyrosine-kinase inhibitors (RTKIs) suppresses the growth of ovarian cancer cells expressing PDGFRα. Data also indicate that there is in-vitro synergism between the PDGFR kinase inhibitor imatinib mesylate (Gleevec) and taxane chemotherapy. Building upon these laboratory observations, Matei and colleagues designed a clinical protocol aimed at patients with refractory ovarian cancer. This protocol utilizes a combination of imatinib and docetaxel in patients with PDGFR expressing ovarian tumors. This trial is currently active at the Indiana University Cancer Center and is open to community practices in Indiana through the Hoosier Oncology group. Several patients have been enrolled and treated on this protocol. The goals of the current proposal are **to identify critical elements of the PDGF-PDGFR pathway responsible for ovarian tumor growth inhibition in-vivo and in-vitro, in**

the context of this clinical protocol. It is clear that PDGFR activation engages a complex signaling network in the cancer cell, which will be turned off by imatinib. Among the mechanisms engaged by PDGFR, Akt plays an essential role as a growth and survival pathway. Preliminary data suggests that constitutive Akt activation induces resistance to PDGFR inhibition in-vitro. **Hence, the investigators of this study hypothesized that Akt-dependent mechanisms are decisive in determining response to treatment targeting PDGFR.**

Matei and colleagues plan to test these two hypotheses by pursuing three objectives: Aim 1: Identify elements of PDGFR activation in tumor specimens and correlate with clinical response. **Aim 2: Define Akt-dependent mechanisms responsible for the effects of imatinib plus docetaxel combination in-vitro. Aim 3: Determine whether activation of Akt impacts sensitivity to treatment with imatinib and docetaxel in-vivo.**

Sweeney Receives RAID Grant to Bring Parthenolide from the Lab to the Cancer Patient

Christopher Sweeney, MBBS, co-leader of the IU Cancer Center Experimental Therapeutics Program and director of Indiana University's Developmental Therapeutics Program, has developed a project to bring a novel cancer-killing compound from the laboratory to cancer patients with the help of a unique program at the National Institutes of Health (NIH) known as Rapid Access to Intervention Development, or RAID.

Sweeney's project, "Bringing Parthenolide from the Laboratory to the Cancer Patient" was accepted to the RAID program. The program is designed to assist with translating laboratory findings to clinical trials of novel anticancer therapeutic interventions.

Many cancer treatments stop cancer cells from dividing and growing, and chemotherapy can hold diseases at bay. However, patients often die when tumor cells eventually develop resistance to the drugs being used; cancer cell mutations occur that allow them to avoid the natural cell death process of apoptosis and permit uncontrolled growth. Modern cancer drug development is looking at designing treatments such as parthenolide that promote apoptosis.

Parthenolide is an attractive drug candidate for a variety of human cancer types. The molecule demonstrates robust tumor specific cell killing of human leukemia, lymphoma, breast cancer and prostate cancer cells, as well as anti-angiogenic activity, a very low toxicity, and strong synergy with several exisiting chemotherapy agents. It is naturally occurring and can be isolated and purified from readily available sources at a very reasonable cost.

Recently other Experimental Therapeutics Program members have demonstrated parthenolide's anti-cancer activity in pancreas cancer (**Max Schmidt, MD, PhD, MBA and Melissa Yip-Schneider, PhD**) and have shown it enhances radiation therapy (**Marc Mendonca PhD**).

Sweeney's work could not have been realized without the essential involvement of **Harikrishna Nakshatri, PhD**, Breast Cancer Program member of the IU Cancer Center, who discovered parthenolide in his breast cancer studies. Nakshatri was the first to demonstrate a role for NFκB in breast cancer. He showed that NFκB activates several cell division genes in breast cancer cells, resulting in enhanced growth, invasion and metastasis. Nakshatri extracted parthenolide from the herb feverfew to show that it inhibits NFκB. He proved that by removing NFκB activity from breast cancer cells, he was able to restore drug sensitivity. Nakshatri and Sweeney will collaborate to transition parthenolide to the clinic as well as evaluate its role in prostate cancer.

Scientific Abstract

Most cancer deaths are due to tumors that are resistant to conventional chemotherapy approaches. Recent advances in understanding the molecular events involved in tumor growth and metastasis offer a unique opportunity to advance beyond these treatment regimens and to produce novel cancer drugs. Cancer cells have developed a wide array of mutations that have largely allowed them to avoid apoptotic mechanisms that permit uncontrolled growth and eventual spread. Consequently, the production of pro-apoptotic drugs has been a feature of modern cancer drug development. As our understanding of apoptotic mechanisms has advanced, several important pathways have received particular attention. Principal targets of pro-apoptotic drugs include NFκB, the Bcl family of related proteins, caspases, and TNF-related pathways. The objective of this proposal is to translate the

potential of a novel and unique pro-apoptotic agent, parthenolide towards human clinical trials. Sweeney and others have demonstrated striking anti-oncogenic characteristics of parthenolide using a variety of *in vitro* and *in vivo* assays. The molecule demonstrates robust tumor specific cell killing of human leukemia, lymphoma, breast cancer and prostate cancer cells, as well as anti-angiogenic activity, and a very low toxicity profile with bioactivity in *in vivo* models. The mechanism of action appears to be by induction of caspase activity via the JNK activation pathway, inhibition of the NFκB pathway, together with upregulation of p21 and blockage of the cell cycle at G2/M. As a consequence, parthenolide has single agent activity and strongly synergizes with several exisiting chemotherapy agents, including taxanes, proteasome inhibitors, the fas-ligand TRAIL, and ionizing radiation. Parthenolide, a naturally occurring sesquiterpene lactone, can be isolated and purified from readily available sources at a very reasonable cost. It can be formulated as either an intravenous preparation or as an orally bioavailable agent, and is an attractive drug candidate for a variety of human cancers.

Prostate Cancer Pilot Projects Awarded to Von Bülow and Giesler

The Central Indiana Prostate Cancer Foundation (CIPCF) in conjunction with the Indiana University Cancer Center funded two prostate cancer pilot projects. A primary goal of the CIPCF and the pilot project funding is to stimulate multi-disciplinary and translational research that will decrease the incidence and adverse impact of prostate cancer.

Götz von Bülow, PhD (Regulation of Cell Growth Program member) received pilot project funding for "Recombinant AAV-TACI vectors for gene therapy of prostate cancer." Co-investigators include **Arun Srivastava, PhD** (Hematopoiesis and Immunology Program member) and **Thomas Gardener, MD** (Experimental Therapeutics Program member). This research will determine whether gene therapy with cell surface receptor TACI is a feasible strategy for the treatment of prostate cancer.

Abstract

Prostate cancer is the second-most common cancer found in American men. The molecular basis of prostate cancer is complex but revolves around mechanisms which control the ability of cells to undergo division. One mechanism of control is the response to secreted factors or hormones. These function by engaging specific receptors on the cell surface which transmit signals to the nucleus. These signals can induce the cell to divide, or die by a mechanism of cell suicide known as apoptosis. Von Bülow and colleagues have determined that a cell surface receptor named TACI is found in normal prostate tissue but is absent in prostate tumor cells. A growth factor named APRIL can bind to TACI, and is made by both normal prostate and tumor cells. Significantly, TACI deficient mice spontaneously develop a precancerous tumor known as prostate intraepithelial neoplasia (PIN). In other cell types, TACI has been shown to antagonize cell growth and trigger apoptosis. The investigators' hypothesis is that the loss of TACI in prostate tumor cells leaves these cells without this control mechanism, thus accounting for the cancer. Von Bülow and colleagues propose to develop viral gene therapy vectors which will restore the expression of the TACI protein in prostate tumor cells with the anticipation that this will kill the cells by apoptosis. This research will determine whether gene therapy with TACI is a feasible strategy for the treatment of prostate cancer.

Brian Giesler, PhD, was awarded pilot project funding for "The Role of Serotonin in Reducing Hot Flashed in Prostate Cancer Patients Undergoing a Program of Resistance Training." Co-investigators include: **Janet Carpenter, PhD, RN, Theresa Damush, PhD and Patrick Monahan, PhD** from the Behavioral Oncology and Research Program; **Todd Skaar, PhD** of the Breast Cancer Program, **Christopher Sweeney, MD** of the Experimental Therapeutics Program, and **Yan Jin, MD and Zeruesenay Desta, PhD** of the Division of Clinical Pharmacology. The study will provide valuable insights into whether and how exercise may reduce hot flash symptoms in men undergoing androgen deprivation therapy (ADT).

Abstract

Men diagnosed with advanced prostate cancer are usually treated with androgen deprivation therapy (ADT), which interferes with the production of male hormones (e.g. testosterone). Because the growth of prostate tumors depends upon circulating male hormones, reducing their levels is an effective means to stop or slow prostate cancer. ADT can thus significantly extend the lives of many patients.

Unfortunately, ADT is associated with several side-effects that can reduce patients' quality of life. Some of the most common are hot flashes, sleep problems, fatigue, loss of muscle tone, increased body fat, nausea and loss of sexual libido and function. Hot flashes in particular are one of the most troubling side-effects of ADT. They can cause significant physical discomfort and psychological distress. About 75% of ADT patients have hot flashed that are severe enough to warrant clinical attention.

Much research has been devoted toward developing interventions that can relieve hot flashes in cancer populations. Although the physiological processes that cause hot flashes are not well understood, a number of studies suggest that the neurotransmitter serotonin plays an important role in the development of hot flashes. Drugs that essentially increase levels of serotonin in the brain, such as antidepressants, seem to reduce levels of hot flashes. However, current forms of anti-depressants are far from 100% effective in reducing hot flashes, have their own side-effects, have yet to be tested rigorously in men undergoing ADT, and may strain the financial resources of some patients. Greater insight into the relationship between serotonin and hot flashes is needed to develop more effective interventions and/or interventions that could complement existing methods of treatment. One way to examine whether serotonin plays an important role in hot flash reduction is to examine whether other types of interventions that increase serotonin also decrease hot flash symptoms.

For example, physical exercise has been consistently linked with increased levels of serotonin in both the short- and long-term, and several studies suggest that individuals who exercise are less likely to experience hot flashes. These findings suggest that men undergoing ADT may benefit from engaging in a program of exercise. Exercise may specifically affect hot flash symptoms by increasing levels of serotonin. Exercise may also benefit ADT patients in other ways by decreasing sleep problems and other side-effects and increasing overall physical and mental well-being.

Giesler and colleagues propose a pilot study to examine the relationship between exercise, serotonin levels and hot flash symptoms in a sample of prostate cancer patients undergoing ADT. The resulting data will be used to support a larger grant proposal. The grant proposal will use a large sample and randomized trial methodology to determine whether exercise reduces hot flashes and other side-effects of ADT and whether serotonin is associated with the anticipated changes in hot flashes. For the pilot study we are currently proposing, ten prostate cancer patients who are undergoing ADT will be asked to complete a three month program of resistance training (e.g. weight lifting). Before beginning the program and then again after its completion, investigators will measure serotonin levels, hot flash symptoms and other side-effects associated with ADT. The primary objectives of the pilot study will be to assess the feasibility of the procedures for the larger study and to determine whether men who exercise exhibit increased levels of serotonin and reduced levels of hot flashes and other symptoms. The resulting information should: 1) greatly increase the likelihood of the larger grant proposal receiving funding and 2) provide valuable insights into whether and how exercise may reduce hot flash symptoms in men undergoing ADT.