NORRIS COTTON CANCER CENTER
2007 PROUTY PILOT PROJECTS

CANCER CONTROL

Trial of Physician Personalized Educational Messages to Address Modifiable Risk Factors for Obesity in Children

Auden McClure and Susanne Tanski

Obesity has become a leading national health care issue in both adults and children. Obesity is a leading cause of certain cancer types including breast, endometrial, esophageal, kidney (renal cell), prostate and colon cancer, and cancer risk can be decreased with moderate weight loss. However, changing established patterns of behaviors such as eating and exercise habits is difficult. Therefore, this Prouty Pilot Project will focus on preventing obesity by addressing early childhood risk factors for it, including television use and excessive sweetened beverage consumption, before children become overweight. We will test whether communications from the child's primary physician to parents of young children will affect attitudes towards these obesity risk factors by conducting a trial in which parents receive three personalized letters from their physician with guidelines about these two risk factors. We hypothesize that their attitudes and parenting behaviors regarding use of television and sweet beverage consumption will shift toward American Academy of Pediatrics recommendations. Through this simple intervention, which can be extended to include other risk factors for cancer, we hope ultimately to decrease the risk for obesity in children and the associated risk for cancer as adults.

Understanding the ENABLE Intervention and "Usual Palliative Care": A Qualitative Interview Study

Marie Bakitas and Mark Hegel

Describe the utilization and perceived value of the ENABLE palliative care intervention from the perspectives of participants and their caregivers. 2. Describe the current standard of "usual care" as provided at the NCCC to patients with advanced cancer and their caregivers.

CANCER MECHANISMS

Development of Nicotinamide Riboside (NR) as a Novel Agent to Reduce Chemotherapy-Induced Peripheral Neuropathy

Charles Brenner, Lionel Lewis, and Alex Pletnev

The dose-limiting side effect of many approved cancer chemotherapies is painful peripheral neuropathy that results from collateral damage to neurons. In the mouse,

increased synthesis of a cellular factor called NAD protects against this nerve damage. Nicotinamide riboside (NR), a novel vitamin discovered by Dr. Brenner, protects neurons in culture and has the potential to improve cancer care for hundreds of thousand of patients who take cancer chemotherapy each year. Support from The Prouty will allow Dr. Pletnev to improve and scale up the synthesis of NR and Drs. Brenner and Lewis to determine the best dosing scheme in order for NR to be safe and efficacious.

RADIOBIOLOGY AND BIOENGINEERING

Electrical Impedance Spectroscopy of Prostate as an Alternative Tool for Cancer Detection

Ryan Halter, Alex Hartov, Alan Schned, John Heaney, and Keith Paulsen

Of all men biopsied for prostate cancer as a result of abnormal findings through screening tests, only one in four is actually diagnosed with cancer of the prostate. This leads to unnecessary anxiety for the majority of men submitted for biopsy and presents a financial burden to the health care system. The primary objective of this research effort is to evaluate the value of electrical impedance spectroscopy (EIS) as a new clinical tool for detecting prostate cancer. In a small group of prostates, we used EIS to show that the electrical properties of malignant and benign prostate tissues differ due to differences in cellular architecture between the tissue types. Here we will be measuring the electrical properties of a larger cohort of prostates to determine how significant these differences are. Based on these findings, clinical EIS probes for detecting and imaging prostate cancer will be designed. These probes will likely be used as adjuncts to current imaging methods, to provide tools for enhancing clinical diagnosis. Further, one could envision using a tool like this to better guide biopsy placement reducing the chance of missing critical regions of the prostate that should be clinically assessed. The EIS imaging tool we ultimately envision consists of a set of electrodes retrofitted to a transrectal ultrasound (TRUS) probe so that coupled EIS and ultrasound measurements can be made. Developing an add-on to accepted clinical tools, like TRUS, will likely make a more immediate impact within the clinic.

Scatter imaging system to detect tumor-associated stroma in breast tissue

Wendy Wells and Brian Pogue

Breast cancer lumpectomy has become the major surgical treatment for localized tumors under 3 cm in diameter. While cure rates from this surgical method are quite good, there are procedural problems in the approach to analyzing the successful lumpectomy resection. If the margins of the lump removed show signs of having tumor tissue, the surgeon must recall the patient the following week for additional surgery to enlarge the resection margin, and at present this recall rate is near 50 to 60% of all cases. The imaging system developed in this grant will allow real time visulation of the optical scattering of the tissue, separated from the absorption due to

blood. Preliminary data has shown that these scatter images should be able to help the pathologist and surgeon determine when there are tumor-involved margins in the lump removed, and then allow them to resect more tissue during the surgical procedure.

Monitoring Tissue Oxygen Change during Tumorigenesis with Multi-Probe Implantable Resonators

Li, H. Hou, Nadeem Khan, and Harold Swartz

Oxygen plays very important roles in the functioning of human beings as well as other living subjects from the microbe, plants to animals. Partial and complete deprivation of oxygen supply and usage in humans, such as the mountain sickness, stroke and heart failure can cause serious health problems. In these cases, a common feature of these abnormalities is a low level of oxygen in affected tissues, which is called hypoxia. In case of brain tumor/cancer, the rapid outgrowth of the cancer tissue over the normal brain regions causes a similar hypoxic state in the center (core) of the cancer. Such hypoxic state promotes the generation of micro-vascular structures, tumor recurrence, resistance to chemotherapy and radiation therapy, and decreased patient survival for many malignancies. So knowing the exact oxygen level in the affected tissue is of clinical importance. Electron paramagnetic resonance (EPR) at 1.2 GHz wave length is a magnetic technique that can be used to measure the oxygen levels in the organs specifically. Such measurement helps the clinical doctors and medical investigators to understand how the cancer develops and progresses in the influenced tissues. It also has the potential to serve as objective tool to the evaluations of the cancer treatment.

To date, EPR has been successfully applied to the studies of tissue oxygenation during cancer development and treatment in laboratory animals. However they are several obstacles, such as the depth (maximum ~10 mm), size of the region of interest, sensitivity, repeatability and bio-compatibility of the oxygen sensing materials limited the wide and efficient use of this excellent technique. In addition, the EPR technique can only investigate the tissue within the EPR external resonator loop. Regions that are bigger than the loop size or scattered here and there in the body can not be surveyed simultaneously. In order to overcome these obstacles, our EPR Center has developed a multi-probe implantable resonator (MPIR) that permit us to target the cancerous tissue deep in the body and measure the tissue oxygen in several sites at the same time. Our data show that MPIR has the ability to measure the tissue oxygen at several brain locations, with good signal strength and repeatability. Further optimization and development of this methodology will enable us to monitor the brain tumor oxygen change precisely and chronically, providing a new tool to aid the diagnosis and treatment of cancers and other diseases.

EPR Oximetry Measurements in Patients Undergoing Free Flap Reconstruction to Assess Tissue Viability

Benjamin Williams, Joseph Paydarfar, Shudong Jiang, Benoit Gosselin and Harold Swartz

Patients who undergo extensive head and neck surgery during cancer treatment will typically undergo a complex reconstruction procedure where flaps of skin, bone, muscle, or viscera with their blood supply are transferred from a distant part of the body. These transferred tissues are closely monitored for signs of insufficient blood supply and oxygenation. If such problems are identified early, then there is an increased likelihood that tissues can be salvaged, either through surgical or pharmacologic interventions. However, current monitoring methods are limited by inter-observer variability and an inability to detect subtle changes. *In vivo* electron paramagnetic resonance (EPR) oximetry and near infrared (NIR) spectroscopy are novel techniques being developed locally to provide such measurements of tissue oxygenation. In this pilot project we will apply these techniques to monitor the viability of transferred tissue during reconstruction procedures which we hypothesize could enable surgeons to perform tissue reconstruction with decreased the rates of complications

IMMUNOLOGY AND CANCER IMMUNOTHERAPY

A Pilot study of ultrasound guided cryoablation of small unifocal invasive breast cancer using contfrast enhanced MRI to evaluate tumor viability and immunologic assays to identify and characterize a cryoablation induced immune repsponse.
Richard Barth

Strategies to induce an immune response to eradicate cancer is an exciting new strategy that could allow for cancer remission and long term protection against relapse. Dr. Richard Barth will test if ultra-sound guided freezing of tumors liberates cancer cell components that can induce immunity to cancer. Using novel, cryoablation technology, Dr. Barth will measure if disruption of tumors in patients by freezing these tumors to extremely low temperatures induces immunity to cancer antigens. If successful, this novel intervention may provide an important new way to induce tumor specific immunity.

Post-exicisional tumor immunity in the liver
James Gorham

The second novel Prouty funded project brings together Dr. Turk's expertise in tumor immunity with Dr. Gorham's expertise in the liver immune system. Highly effective immunity to melanoma cells can be generated to prevent spread of tumor cells to other sites in the skin. However, the development of metastases to internal organs, such as the liver, represents the principal threat to survival in melanoma patients. Surprisingly little is actually known about whether effective tumor immunity can extend to metastases that arise in the liver, since the liver is known to suppress immune responses. In this project, we will ask whether the liver suppresses immunity to melanoma cells using a well established system in mice. The results should have important implications for melanoma patients, for whom metastases represent the biggest hurdle to their long-term survival.

MOLECULAR THERAPEUTICS

The development and validation of an assay for the quantitation of conjugated linoleic acid in human tissues.
Lionel Lewis, William Kinlaw and Ray Perez

Conjugated linoleic acid (CLA) is consumed by humans as a dietary supplement and is also fed to animals to reduce the fat content of milk. It has also been shown in experimental models to reduce the incidence of cancer. However, virtually no data are available regarding the amount of CLA that would need to be consumed to have a anti-cancer effect. Laboratory research of Dr. Kinlaw has established a novel mechanism of action for CLA which involves suppression of fatty acid synthesis in the tumor, and as a consequence inhibition of tumor growth. These results have led to a collaboration between Drs. Kinlaw, Lewis and Perez to determine whether the amounts of CLA normally consumed are sufficient to inhibit this critical pathway in humans. This Prouty Pilot grant will recruit healthy volunteers who will provide blood and fat tissue for assay. Once appropriate dose and schedule of administration have been established, subsequent studies will investigate the potential therapeutic effect of CLA in cancer patients.

Role of Hedgehog in vascular smooth muscle cell recruitment in angiogenesis
Kathleen Martin and David Robbins

Dr. Martin investigates the mechanisms by which blood vessels grow in a tumor, a process that is essential to provide oxygen and nutrients to the growing tumor. The cells in blood vessels are well differentiated and do not normally grow. However, when called upon by the needs of the tumor, they dramatically change and begin to grow and migrate into the tumor. New information has suggested that one of the important regulators of the growth of these blood vessel cells is a novel signaling pathway known Hedgehog. The Hedgehog pathway has been extensively studied by Dr. Robbins, and hence these two investigators will now collaborate in a project to determine whether the Hedgehog pathway is critical for the growth of tumor blood vessels, and whether novel compounds under investigation in Dr. Robbins laboratory can impede this growth and thereby control tumor growth.

Identification of drug targets in tumor cells defective in NF1
Yolanda Sanchez

Mutations in the Neurofibromatosis type 1 gene (NF1) causes a disease that affects 1:3500 live births that almost invariably results in neurofibromas. In about 10% of these patients, the disease progresses to malignant peripheral nerve sheath tumors for which there is no effective therapy. Dr. Sanchez proposes to search for compounds that selectively kill cells defective for NF1. She has developed a yeast model with the same genetic defects as the human disease, and will use this model to screen thousands of chemicals for their ability to inhibit growth of the yeast. Using yeast

genetics, she will then be able to identify the target for these compounds, and extrapolate back to the human situation to establish that this is also a valid target for killing human cells with NF1 defects. Subsequently, she will be able to identify drugs that inhibit the human target and are effective against the human disease.

CANCER ONCOLOGY PROGRAMS

Identification of a Novel Effector of Wnt Signaling in the Pathogenesis of Colorectal Carcinoma

Yashi Ahmed, David Robbins, and Amitabh Srivastava

In the colon, dysregulation of genes in the "Wnt" pathway is a common event in the development of cancer. Dr. Ahmed's laboratory studies these genes in fruitflies and has discovered new players that could be important in human cancer. In collaboration with Dr. Robbins, she will determine whether human proteins that correspond to her fly proteins interact with each other. In collaboration with Dr. Srivastava, she will examine the expression of these proteins in human cancers. Thus, support from the Prouty is moving basic science toward deeper understanding of the causes of and potential specific treatments for colon cancer.

Interaction between Tobacco Smoke Exposure and Cyclin E Overexpression in Lung Carcinogenesis in Mice

Steven FierinG, Mardi Crane and Ethan Dmitrovsky

Tobacco smoke is the largest contributor to lung cancer, the most lethal of all cancers. Using a mouse model of lung cancer constructed by Dr. Dmitrovsky, Drs. Fiering and Crane will test the hypothesis that tobacco smoke accelerates cancer development in the mouse model and will determine the mechanisms of smoke-induced carcinogenesis. In this system, Prouty dollars are allowing scientists to dissect the specific effects of environmental toxins in order to identify disease earlier and prevent unnecessary cancer deaths.