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CANCER RESEARCH CENTER

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Order of the Eastern Star Leads the Way!



CRC board president, Randall Johnston presenting Billie Kraemer, Past Grand Matron of the Order of the Eastern Star with an appreciation plaque.

The Order of the Eastern Star was honored in a reception on December 18, 2000 in the William Whitlow Conference Room at the Cancer Research Center (CRC). This event was in appreciation for the dedication to fighting cancer this organization has demonstrated throughout the years.

At the reception, Billie Kraemer, Past Grand Matron (1998-1999) of the Order of the Eastern Star, Grand Chapter of Missouri, presented CRC board president, Randall Johnston, with a check from their annual fundraising efforts. Serving as Worthy Grand Patron during this period was Larry Albright.

The 2000 allocation to CRC was for \$12,912.24. This donation brings the Order of the Eastern Star's all-time contributions to CRC up to \$569,559.57, which sets the pace for CRC giving from an organization.

Kraemer commented, "It was my pleasure to name the Cancer Research Center as one of my charities. It is my sincere wish that someday this dreaded disease will be conquered and it would be very satisfying to know that we helped, if only in a small way."

According to Kraemer, Paul Lineberry, current CRC board member and Past Grand Patron of the Order of the Eastern Star, was very helpful in providing information regarding CRC and its recent advances.

CRC's extensive cancer research is funded in large part by the businesses, citizens, and organizations of Missouri communities, who like the Order of the Eastern Star, desire a solution to this lethal disease. CRC is very appreciative of the Order of the Eastern Star, and thanks them for their many years of continued support.

Your Donations at Work as CRC Scholarships

With your financial contributions, the Cancer Research Center (CRC) is able to provide scholarships to many outstanding students to work along side our experienced scientists. During the past summer, CRC added two talented student employees to its cancer fighting team.

In June, Breca Starr Tracy, a junior at Stephens College became CRC's fifth recipient of the prestigious Director's Scholarship. Tracy is currently working on a B.S. degree in Biology and Health Sciences. She plans to earn dual M.D. and Ph.D. degrees so that she may become a research scientist.

Tracy has a 3.5 Grade Point Average; is the President of Stephens' Junior Class; Vice-President of the Beta Beta Beta Biological Honors Society; and captain of the college's tennis team. She recently received Stephens College's prestigious Roeschlaub-Trustee Award, and was nominated for the college's Alumnae Association Scholarship, Staff Advisory Council Scholarship, and Outstanding Underclass Biology Major Award.

The Director's Scholar Fund was established by Dr. Abraham Eisenstark. Dr. Eisenstark currently is CRC's Director for Research. Prior to this, he served as CRC's Director for ten years. Dr. Eisenstark is also a Byler Distinguished Professor (Emeritus) and former Director of Biological Sciences at the University of Missouri-Columbia.

As Director's Scholar, Tracy is systematically surveying as many as 95 possible gene defects in cells. She is sorting out which mutations occur with high probability, and which of the 95 are very stable with rare or no mutations.

In July, CRC awarded the First National Bank & Trust Company Staff Charitable Fund Student Fellowship Award to Caryn Michelle Alderson. Alderson, a graduate of Columbia's Hickman High School, currently is a junior majoring in Biology at the University of Mis-



Pictured from left to right, Breca Starr Tracy and Caryn Michelle Alderson



Continued on page 2

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souri-Columbia and has a 3.6 Grade Point Average.

Since 1999, CRC has been the recipient of a generous annual contribution by the First National Bank & Trust Company Staff Charitable Fund. This is the third year CRC has been designated to receive funding from the bank located in Columbia, Missouri. CRC has established the First National Bank & Trust Company Staff Charitable Fund Student Fellowship Award, in which CRC uses restricted research funds to match this contribution and applies the total amount to this student fellowship. This award will be renewed on an annual basis as funding is available.

At CRC, Alderson is exploring the nature of chromosomal mutation by studying the effects of long-term starvation of cells. She is also studying the susceptibility of cells to infection by bacteriophage as a means of molecular subtyping.

Dr. Kelly Edwards, CRC Senior Scientist, supervises Tracy's and Alderson's cancer research at CRC. According to Dr. Edwards, "These types of scholarships are not only invaluable to CRC and the cancer research we are performing, but they also greatly assist our students with their career goals." She continues, "Both of these women have aspirations to go to medical school and to eventually become doctors. Their internships at CRC will clearly enhance their chances to get accepted into medical school and will make them better doctors in the long run."

Tracy states, "I am thankful for the opportunities that CRC is providing me. I have been introduced to various scientific techniques and research that will help prepare me for my future." Alderson adds, "My grandmother died from cancer, so I am very proud to play a role in CRC's battle against this awful disease."

Tracy, Alderson, and other CRC staff members are available to share their knowledge of cancer research, prevention, detection, and treatment with area groups. There is no charge for these presentations, and you may schedule one by calling Ron Schmidt at (573) 875-2255.

Cancer has affected all of our lives in one way or another. We are dedicated to continue our support to help Cancer Research Center win the battle against cancer.

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Volunteers Key to Helping CRC Fight Cancer



CRC volunteers from left to right, Emily Brady, Ann Bozarth, Lee Freese, and Myrtle Rapp.

More than 60 friends of the Cancer Research Center (CRC) attended the annual appreciation reception on December 4, 2000 at the Peachtree Banquet Center where they saw Emily Brady and Ann and Jack Bozarth recognized as the 2000 Volunteers of the Year, an honor CRC has bestowed on individuals since 1997 in appreciation of their dedication and generosity in furthering cancer research. Past CRC Volunteer of the Year winners include:

- | | |
|------|-------------------------------------|
| 1999 | Carole Newman, Steve Lee |
| 1998 | Billy and Myrtle Rapp, Lonnie Tapia |
| 1997 | Larry Atterberry and family |

Besides the honored volunteers, it was stressed by speakers Ron Schmidt and Jim Cherrington of CRC that everyone in the room was key to the success of local cancer research.

Both Emily and Ann have been very instrumental in the past success of the annual Jim Kidwell Gala, CRC's major fund-raiser. This annual gala is named in memory of Jim Kidwell, a long-time loyal and dedicated supporter of CRC. Jim, a life-long Boone County resident, succumbed to cancer in 1990. He worked tirelessly with this annual event before it was named in his memory. Much of what this banquet has become and the much needed funding received for cancer research is directly attributable to Jim, his hard work, and his cheerful personality.

This year's event will be held on Saturday, March 3 at the Peachtree Banquet Center, and is being dedicated in memory of Clifford Hirst, Raymond Freese, and Jim Kidwell. It will have casino-style games; live and silent auctions; live music provided by the Norm Ruebling Band; raffles; and heavy appetizers. It promises to be a good time for all who attend. For more information about this upcoming event, please call Ron Schmidt at (573) 875-2255.

Your Donations Lead to Reduced Cancer Deaths...



A number of promising new strategies are being developed by Columbia scientists for the prevention, diagnosis, and treatment of cancer. The Cancer Research Center (CRC) provides additional funds for their projects.

THE SCIENTISTS AND THEIR STRATEGIES INCLUDE:

1. Radiopharmaceuticals to target and destroy tumors. In this strategy, developed at the University of Missouri, drugs are linked up with radioactive metals that specifically attach to tumor cells. First, this can provide a visual image to pinpoint the tumor. Next, the energy emitted from the radioactive metal can then destroy tumor cells. These are the investigators who receive CRC support and who utilize this strategy, and their description of their research.

■ **Radiolabeled Peptides and Fab that Target Prostate Specific Membrane Antigen: New Prostate Cancer Therapeutics**

*Dr. Susan Deutscher, CRC award recipient;
Dr. Linda Landon, Postdoctoral Fellow*

This research focuses on the identification and development of therapeutic and diagnostic peptides and antibodies that specifically recognize and bind to molecules that are expressed on the surface of prostate cancer cells and other adenocarcinoma cells but that are not expressed on normal cells. By specifically binding to cancer cells but not normal cells, the peptides and antibodies, which will be labeled with a radioactive atom, will contribute to the early diagnosis of primary adenocarcinoma cancers, such as prostate cancer, and can be used therapeutically to specifically deliver the radioactive atom to cancer cells in both primary and metastasized lesions. Prostate cancer that is detected early (before the tumor cells metastasize and spread to other areas of the body) has the highest rate of being cured. However, current prostate cancer cells have occurred and do not identify the location in the body of the metastasized cells. In addition, there are no reliable anti-prostate cancer therapies to use to identify and destroy metastasized prostate cancer cells. Dr. Landon, Postdoctoral Fellow, has recently shown that peptides and antibodies which specifically bind to the disaccharide Thomsen-Freidenreich antigen (T antigen) can differentiate between cultured cells derived from prostate and breast adenocarcinomas, on which T antigen is exposed, and non-adenocarcinomas cultured cells, on which T antigen is not exposed. Future experiments will be conducted to determine the ability of the reagents to distinguish T antigen from other closely related disaccharides. Currently, Dr. Landon is labeling the peptide and antibody reagents with radioactive atoms so that the reagents can be injected into mice, which have experimentally-induced tumors, order to observe the pharmacokinetic and pharmacodynamic characteristics of the reagents.

Bottom Line - This targeted therapy linking radioactive isotopes with drugs should lead to earlier diagnosis as well as destruction of tumor cells.

■ **Pancreatic Cancer**

Dr. Tim Hoffman, CRC award recipient

Pancreatic cancer is currently the fourth leading cause of cancer mortality in the United States. Present limitations in conventional chemotherapy speak to the need to develop new therapies, coupled with improved diagnostic strategies, to enhance quantity and quality of life in patients diagnosed with pancreatic cancer. The research project being conducted with CRC holds the potential for development of one or more radiolabeled Gastrin Releasing Peptide (GRP) receptor-avid pharmaceuticals, that will be effective site-directed agents, for the diagnosis and/or treatment of patients with localized, as well as metastasized pancreatic cancer. Using appropriate radioisotopes for diagnostic purposes, one can prepare radiolabeled compounds with targeted radiodiagnostic/radiotherapeutic capabilities.

Bottom Line - Using this selective targeting approach should lessen the toxic effects of drugs that are in current use.


■ **Malignant Melanomas**

Dr. Thomas Quinn, CRC award recipient


Malignant melanoma has become a serious public health problem due to an increase in incidence and the difficulties in discovering and treating melanoma metastases. Malignant melanoma is the eighth most common cancer in the U.S. In 1993, there were 6,800 deaths due to malignant

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melanoma and 32,000 new cases reported. Currently, 1 out of 105 Caucasians will develop malignant melanoma, and the rate is projected to be 1 out of 75 by the year 2001. Early melanoma tumor diagnosis and prompt surgical removal are a patient's best hope for a cure. Metastatic malignant melanoma is resistant to current chemotherapeutic and immunotherapeutic drugs. Combinations of chemotherapeutic agents or chemo/immunotherapeutic agents offer the best response rates. Despite recent advances in combination therapy regimens, the median survival for patients diagnosed with metastatic malignant melanoma is approximately six to nine months, with less than 10% surviving five years or more.

We have developed a novel family of peptide-based radiopharmaceuticals cyclized through the coordination of radiometals, that target a receptor present on the surfaces of malignant melanoma tumor cells. We have examined its tumor imaging properties in a mouse melanoma model system. The mouse image clearly shows high activity uptake in the melanoma tumor with very low background levels in the rest of the mouse.

Bottom Line - This targeted therapy linking radioactive isotopes with drugs should lead to earlier diagnosis as well as destruction of tumor cells.

■ **Diagnosis and Treatment of Cancers**

Dr. Kattish Katti, CRC award recipient

Although a number of modalities are available for diagnosis of cancer, there is a need for the development of more selective diagnostic agents which can detect primary sites, identify sites where it has spread (metastatic sites), guide surgical interventions, and monitor efficacy of therapeutic agents to improve patient outcomes. In this context, receptor based site-specific ^{99m}Tc-labeled radiopharmaceuticals provides emerging diagnostic tools which can fulfill these needs.

Receptor based site-specific radiopharmaceuticals, when prepared with a suitable radioisotope, are also useful in the treatment of cancer. They can localize with high specificity at primary as well as secondary cancer sites, even when their location in the body is unknown. Therapeutic radiopharmaceuticals that specifically target tumors will deliver high radiation doses to the tumor while producing minimal radiation damage to the normal tissue. This would make them more effective than existing external beam radiotherapy. Hence, site-specific radiopharmaceuticals could be called "magic bullets" due to their potential efficacy in selective eradication of cancer.

Bottom Line - This targeted therapy linking radioactive isotopes with drugs should lead to earlier diagnosis as well as destruction of tumor cells.



2. Basic understanding of what triggers chromosome damage and the repair of that damage. Although there are dozens of different kinds of cancer, all of them have one thing in common. All tumors are initiated by damage to DNA. Fortunately, cells have repair mechanisms for repair of this damage. However, in some cases, damage is too great or repair is inadequate and cancer develops. These are the investigators who study DNA damage and repair, and their description of their research.

■ **Study of Cytoskeletal Targets for Prevention of Cell Division During Cancer**

Dr. Heide Schatten, CRC award recipient

While some progress had been achieved in recent years to inhibit cell division with taxol, this treatment is not ideal because of the unwanted side effects associated with taxol. The goal of our research is to inhibit very specifically cell division in cancer cells which will destroy only cancer cells without interfering with cell metabolism in healthy tissue. For this approach we have undertaken studies in a transgenic mouse (TRAMP) model and in the prostate cancer cell lines LNCaP and DU145 to investigate the molecular mechanisms during cell division that specifically distinguish cancer cells from normal cells. For technical reasons, our investigations specialize in prostate cancer but will also benefit cancers of the breast, lung, liver, and other affected organs.

We have focused on the cell organelles which are crucial for cell division. Centrosomes are composed of highly specific proteins which are responsible for precisely organizing the distribution of cellular material to the two daughter cells after cell division. One of the problems during cell division in cancer is that centrosome proteins are imbalanced, which results in imbalanced and unequal cell divisions. This sets up cycles of no return into the resting stage of the cell cycle. In order to control cancer it is crucial to assure a precise regulation of centrosome proteins.

Bottom Line - These approaches are preferable over unspecific arrest of cell division with current anti-mitotic drugs such as taxol.

■ **Cancer: A Balance Between DNA Damage and Repair**

Professor Stephen Alexander, CRC award recipient

DNA, the genetic material of all living organisms is constantly subjected to damage from ultraviolet light and chemicals. In animal cells, unrepaired damage can result in mutations and ultimately cancer. Indeed, skin cancer due to overexposure to sunlight is one of the most prevalent forms of cancer in the world. Fortunately, cells of all organisms have mechanisms for repairing damaged DNA. Several repair mechanisms have been identified in animal cells and they seem to be biased towards the type of DNA damage. However, little is known about how the cell senses the type of DNA damage and how it elicits the correct response to the damage. Solving this problem remains one of the most important challenges in cancer biology today because the solution will provide clues to novel detection methods and therapies.

In addition to mutants that are hypersensitive to DNA damage, we also expect to obtain mutants that repair DNA damage better than normal cells. These mutants may define another class of genes and have great potential for investigating the response to other DNA damaging agents including chemicals and other types of radiation.

We expect to identify several genes involved in the response to UV light induced DNA damage. We can immediately determine how these genes are regulated and whether they are involved in the response to other DNA damaging agents or are specific to UV damage. Virtually nothing is known about the mechanisms that animal cells use to protect themselves from cancer by repairing damaged DNA.

The identification of these protective mechanisms will allow many possibilities for developing new diagnostic protocols, as well as novel therapeutic drugs that intervene at specific steps of the pathway.

Bottom Line - By identifying the chemical and immunological structure of critical cell components, superior drugs can be developed to specifically destroy those cell components that lead to runaway growth of tumors.

■ **Genes that Regulate Synthesis of Anti-Oxidant Enzymes that Avoid or Repair Cancer-Causing Damages to DNA**

Professor Abraham Eisenstark (in collaboration with Associate Professor Miriam Golomb and Research Assistant Professor Michael Calcutt)

Oxidants are like molecular bullets that can damage chromosomes, thus capable of initiating tumors. These oxidants are present in certain foods, present in ultraviolet rays of the sun, and are produced in cells as a result of normal metabolism. Fortunately, cells also produce anti-oxidants and anti-oxidant enzymes that can both destroy oxidants and repair damaged chromosomes. In addition, foods that contain anti-oxidants such as vitamin C, vitamin E, and selenium are important in countering damaging effects of oxidants.

Our research has focussed on understanding how regulatory genes are involved in the synthesis of anti-oxidant enzymes and DNA repair enzymes. One of our earlier discoveries [with Professor John McCormick] was that ultra-violet B radiation from the sun produced oxidants that can cause skin cancer. Because of the recognition of the oxidative effects of sunlight, sunscreens now contain anti-oxidants to combat these harmful effects.

Bottom Line - Basic knowledge of the damaging effects of oxidants and the role of anti-oxidant enzymes should lead to the reduction of cancer incidents.

■ **Finding Key Proteins that Regulate Cell Growth and Death**

Dr. Mark Hannink, CRC award recipient

This research involves the understanding how the activity of proteins implicated in cancer is controlled. Many genes and their encoded proteins have been implicated in cancer, and our laboratory works on one group of these proteins, termed the Nuclear Factor kappa B transcription factor. This group of proteins, also known as NF-B for short, is a key regulator of both cell division and programmed cell death. As cancer cells arise when cell division is inappropriately stimulated and programmed cell death pathways are shut off, the NF-B proteins are important modulators of cancer development.

We will characterize two mechanisms that control the activity of NF-B proteins. One mechanism is through inhibition of nuclear import of NF-B.

Continued on page 6



“There are no such things as incurables; there are only things for which man has not found a cure.”

-Bernard M. Baruch



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Symptoms of Cancer

- changes in bowel or bladder habits
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- unusual bleeding or discharge
- thickening or lump in the breast or any other part of the body
- indigestion or difficulty swallowing
- obvious change in a wart or mole
- nagging cough or hoarseness

It is important to see a doctor if you have any of these symptoms.

Continued from page 5

In normal cells, NF-B is retained in the cytoplasm through association with an inhibitor protein, known as IB. However, in various types of cancer, IB is no longer able to inhibit nuclear import of NF-B, with the result that NF-B is able to enter the nucleus and activate expression of growth-stimulatory and anti-cell death genes. This research will enable us to understand how association of NF-B with IB leads to a block in nuclear import of NF-B.

Our laboratory has recently discovered a second regulatory mechanism whereby IB controls NF-B. In particular, we have shown that IB is able to export NF-B from the nucleus. This nuclear export function of IB is part of a feedback inhibitory loop that keeps NF-B activity under control. A second focus of this research will be to dissect the molecular mechanism(s) that are responsible for IB mediated nuclear export of NF-B.

What is the potential impact of this research for reducing cancer incidence and deaths? As NF-B activation occurs in response to a large number of cancer-causing agents, including DNA-damaging agents such as UV irradiation.

Bottom Line - This research will lead to a better understanding of how regulation of NF-kB activity can be restored and thereby interfere with the development of cancer cells.

■ Role of Estrogens in Cancer Control

Professor Dennis Lubahn, CRC award recipient

Breast cancer is one of the leading causes of death among women with approximately one in nine contracting some form of this disease within her lifetime. It has been known for some time that certain types of breast cancers require estrogens for proliferation. This observation has led to a therapy based upon the administration of an estrogen antagonist such as tamoxifen over time, rendering such treatment ineffective. This leads to the development of a tumor that is no longer estrogen responsive. The development of estrogen resistance leads to two central questions. First, what makes some cancers halt cell division in response to estrogen? Second, how do the cancerous cells develop a resistance to this treatment? The answers to these questions are key to developing an effective therapy for many types of breast cancer.

We use specific approaches to identify proteins involved in estrogenic responses in an attempt to isolate a putative estrogen receptor (ER-). The first approach will use the lactoferrin gene promoter that responds to methoxychlor, and estrogenic compound, in an unusual manner.

Identification of all of the receptor proteins involved in the estrogen response of cells is the fundamental first step to understanding how interactions can occur to affect the tumor progression. Such understanding will lead to positive treatments for hormone-responsive cancers through use of selective estrogen agonists and antagonists to specific receptors. This type of targeted therapy would be a more effective alternative to currently available therapies in the fight to control breast cancer and other estrogen responsive tumors.

Bottom Line - This targeted therapy would be a more effective alternative to currently available therapies in the fight to control breast cancer and other estrogen responsive tumors.

3. Destruction of tumor cells with novel drugs and toxins. The search is still on for much better therapeutic agents to destroy cancer cells.

■ Determination of the Role of Estrogen in Colon Cancer Development Using Estrogen Receptor Knockout Mice

Dr. Ruth S. MacDonald, CRC award recipient;

Ju-Yuan Guo, Postdoctoral Fellow

There is increasing evidence that estrogens and phytoestrogens (plant compounds with estrogen activity) affect colon cancer risk. Some evidence suggests that these compounds protect against colon cancer while other evidence suggests they promote colon cancer. The recent widespread availability of phytoestrogen supplements and the promotion of these compounds as safe alternatives to estrogens for treatment of menopause symptoms raise concern of potentially increasing risk of colon cancer. Since colon cancer continues to be a significant cause of cancer related deaths, it is critical to rapidly define the role of estrogen and phytoestrogens in the development of colon cancer. The relationship of estrogens and phytoestrogens to colon cancer is confusing because these compounds can affect cellular behavior through estrogen receptor mediated mechanisms and through non-receptor mechanisms. Additional confusion arises because the different estrogens and different phytoestrogens cause multiple non-estrogen receptor responses. This research will determine if estrogen, conjugated estrogens, genistein, or a mixture of isoflavones alter chemically induced colon cancer in mice. Estrogen receptor mediated responses versus non-estrogen receptor responses will be sorted out by utilizing genetically altered mice that lack estrogen receptors and mice with estrogen receptors.

Genistein and a mixture of soy isoflavones will be used because they are the most widely touted phytoestrogens for reduction of menopause symp-

toms, cancer, and cardiovascular disease. The response to conjugated estrogens, similar to those used in hormone replacement therapy for women, will also be tested. Moreover, changes in enzyme and gene activity in colon cells will be correlated with changes in colon cancer to increase our understanding of cellular events leading to cancer.

Bottom Line - Specific plant foods may have a significant role in prevention of cancer.

■ **Characterization of the Gene that Controls Expression of a Protein Important for Cancer Cells to Spread from the Site of the Original Tumor**

*Dr. William Folk, CRC award recipient;
Dr. Kimberly A. Lieber, Postdoctoral Fellow*

DNA, the genetic material of all living organisms is constantly subjected to damage from ultraviolet light and chemicals. In animal cells, unrepaired damage can result in mutations and ultimately cancer. Indeed, skin cancer due to overexposure to sunlight is one of the most prevalent forms of cancer in the world. Fortunately, cells of all organisms have mechanisms for repairing damaged DNA. Several repair mechanisms have been identified in animal cells and they seem to be biased towards the type of DNA damage. However, little is known about how the cell senses the type of DNA damage and how it elicits the correct response to the damage. Solving this problem remains one of the most important challenges in cancer biology today because the solution will provide clues to novel detection methods and therapies.

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Bottom Line - The identification of these protective mechanisms will allow development of new diagnostic protocols, as well as novel therapeutic drugs.

■ **An Application Toward Deciphering Epigenetic Signatures of Breast Cancer**

*Dr. Tim H.-M. Huang, CRC award recipient;
Huidong Shi, Postdoctoral Fellow*

Cancer is a complex disease, resulting from multiple genetic mutations of genes. One less known phenomenon is epigenetic mutation also frequently observed in cancer. This epigenetic mutation occurs by converting cytosine bases (Cs) to methylated Cs (mCs) via a chemical reaction, called DNA methylation. Because of this epigenetic imbalance, gene regulation specific for a cell type is disrupted, leading to tumor formation. In this project, we will develop a special technique using the so-called DNA chip technology for simultaneous analysis of methylated Cs across thousands of genes in cancer cells. Our approach can generate a vast amount of information for unique molecular identifiers, i.e., epigenetic signatures, of individual cancers.

Bottom Line - This study will pave the way for complementing the histopathological examinations currently in use with molecular diagnosis and classification of tumors.

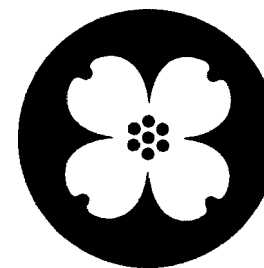
■ **Does Developmental Exposure to Environmental Estrogens Increase Risk for Prostate Carcinogenesis?**

*Dr. Frederick S. vom Saal, CRC award recipient;
Catherine Richter, Postdoctoral Fellow*

Mouse fetuses will be exposed to estrogenic chemicals which leach out of plastic bottles and food containers, and the effects on the subsequent development of prostate cancer will be determined using a mouse strain that develops prostate cancer that is similar in many respects to prostate cancer in men.

Exposure during fetal life to estrogenic drugs has been shown to result in prostate cancer in animal studies, and has been related to vaginal cancer in women. However, our studies will be the first to examine the possibility that exposure during fetal life to estrogenic chemicals used to make plastic products is related to subsequent prostate cancer onset and progression.

Bottom Line - This study will identify whether certain chemicals alter estrogen in fetal life and lead to prostate cancer in adults.



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Development Director's Note



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CRC is not affiliated with any national organizations, so we are not obligated to forward any portion of the contributions we receive to any governing body. All gifts stay in Columbia, Missouri and assist our scientists in their battle against cancer. This allows our donations, no

matter how big or small, to make a greater difference than they might elsewhere.

As our scientists learn more about tumors, they turn that knowledge into a weapon. For years there were three ways you could address a cancer. You could poison it with a drug (chemotherapy), you could kill it with energy (radiation), or you could cut it out (surgery).

Because of the comprehensive studies that are being conducted at CRC, we are going way beyond poisoning, radiating, and cutting out cancer cells. We are developing procedures to stop cancer before it ever starts and techniques to treat it that avoid destroying or removing good cells along with the cancerous ones.

These research advances were made possible through donations from those individuals, businesses, and organizations listed throughout this newspaper. On behalf of the Board of Trustees and the entire staff at CRC, I would like to express our appreciation for their generous support.

Together, we can put an end to cancer and the devastation it causes.

Sincerely,

Ron Schmidt

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Erma Lee Pryor

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■ CLINTON, MO

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TRIBUTE TO**
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Orville Livingston, PGP
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Grand Chapter
Pleasant Dale Club
St. Peters Lutheran Social
Club



*"The family suggests that
memorial contributions be made
to the Cancer Research Center."*



**When people want to honor
a loved one and fight cancer.**

Pamela Dunn Legacy of Hope

Many fine minds have contributed to cancer research. At the Cancer Research Center (CRC), we honor the memory of one of our own — Dr. Pamela Dunn. Dr. Dunn died in 1983 from the very disease she sought to conquer through her work in microbiology. She had participated in several important breakthroughs in cancer research. Her work was both scientific and humanitarian, with a genuine concern for the cancer patient and the trauma he or she experienced.

In 1981, Pamela Dunn was diagnosed as having a rare form of breast cancer. For many months, she was both research subject and

scientist, adding to our knowledge of the disease which had perversely selected one of its prime opponents.

Despite all possible measures, she lost her personal battle against cancer. However, her work continues through the Pamela Dunn Legacy of Hope. The Pamela Dunn Legacy of Hope was established to honor her commitment in the fight against cancer. This special fund provides the financial backing necessary to ensure that her work can be completed. The gifts to the fund remember and honor not only Dr. Dunn, but the thousands of Missourians who die each year of cancer.

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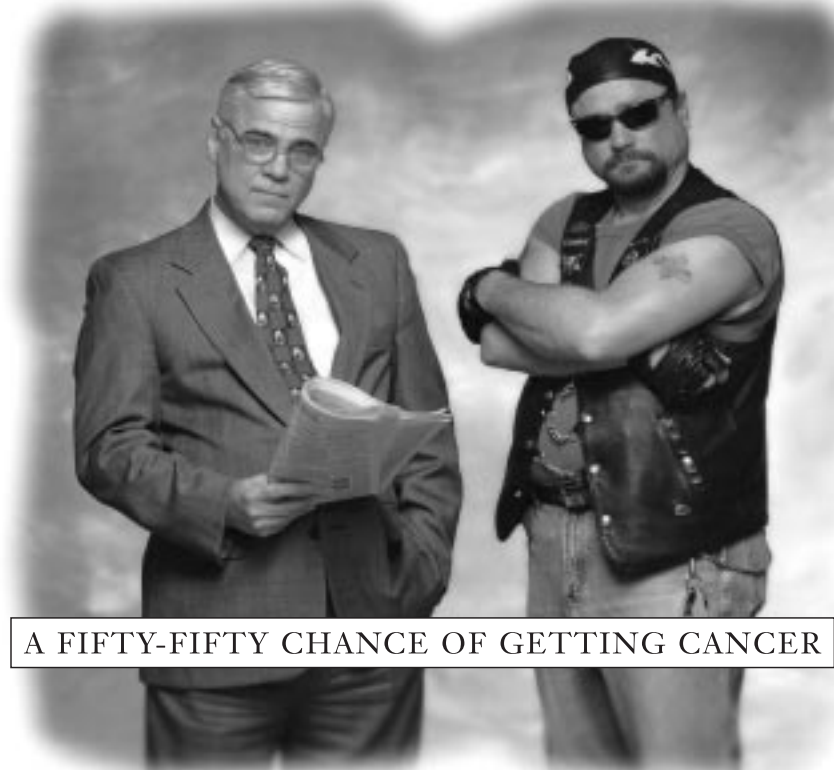
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■ **Novel Ways to Inhibit the Growth of Cancer Cells**

Dr. Gary Weisman, CRC award recipient

A major emphasis in the development of new cancer treatments is to devise novel ways to inhibit the growth of cancer cells, thereby preventing tumor formation. Another effective approach is to employ cancer treatments that increase the rate of tumor cell death. We are studying a family of proteins called nucleotide receptors that are present in a variety of tissues. Evidence suggests that a specific nucleotide receptor called P2X, functions to promote tumor cell death. We are investigating this protein at the molecular level to understand how it kills cancer cells. Another nucleotide receptor called P27, functions to increase the growth of blood vessels that accelerate tumor formation. By studying P2Y receptors, we hope to learn how to prevent them from stimulating blood vessel growth, so that we can promote tumor regression. Thus, the nucleotide receptor family offers promising new targets for cancer therapy that require further investigation.

Bottom Line - This strategy of blocking blood vessel growth increases the probability of destroying tumor development.



■ **Exploration of Bacterial Toxins for Use as Chemotherapeutic Agents**

C.W. Caldwell and Kelly Edwards, Postdoctoral Fellow, CRC Laboratory Associate

Bacteria are capable of producing toxins that can be used in beneficial therapeutic applications in both human and animal medicine. Specifically, certain strains of Escherichia coli have been shown to express Shiga toxins that have demonstrated anti-cancer properties. Subsequent investigation has shown that Shiga toxin type I is the agent responsible for the anti-cancer activity. Ovarian carcinoma cell lines were found to be highly susceptible to the killing effects of the toxin in laboratory experiments. The toxin also has the ability to cross the blood-brain barrier in humans, which facilitates the ability to attack certain

types of brain tumors. Cancerous cells are specifically targeted for killing through the expression of a unique receptor molecule on the cell surface which is not typically found on normal healthy cells except in the kidney.

The specific aim of this project is to survey various tumor types for expression of the toxin receptor and therefore sensitivity to the killing effects of the toxin. This objective will be accomplished with an interdisciplinary approach. Molecular biology will be utilized for analysis of the purified toxin and the mechanisms involved in targeting the toxin to cancerous tissues. Electron microscopy will facilitate the survey of various cell types for the expression of the toxin receptor using antibodies for detection. Finally, cell culture systems will allow the study of the specific interaction of the toxin with susceptible cells. The exploration of this phenomenon will allow a potent bacterial toxin to be used in a beneficial way as an alternative to other methods of chemotherapy which have potentially devastating effects for cancer patients.

Bottom Line - Naturally occurring, highly targeted chemotherapeutic compounds may be less physically harmful to cancer patients.

4. Development of synthetic vaccines and antibodies.

■ **Chemical and Biochemical Reactions of Dithiolethiones**

Dr. Kent Gates, CRC award recipient

We are seeking to understand the chemical and biological mechanisms by which synthetic and naturally occurring compounds (such as those found in foods like broccoli and cauliflower) can PREVENT cancer in humans.

Bottom Line - An understanding of how these "ANTI-carcinogenic" compounds prevent cancer will ultimately allow us to rationally design cancer-preventive diets and dietary supplements.

■ **Ultrasonic Detection and Characterization of Endocrine Responsive Cancers**

Dr. Steven P. Neal, CRC award recipient; Thad Wilson, Postdoctoral Fellow

In collaboration with Dr. Boote from Radiology at MU, Dr. Neal will use the CRC Fellowship to support the investigation of ultrasonic scattering processes in cancerous and benign prostate tissue. The long-term goals of the research include improving the effectiveness of ultrasound guided needle biopsies of the prostate and ultrasound based screening for prostate cancer.

Bottom Line - This innovative technique will lead to improved diagnostics, as well as to reduce anxiety of the patient.

■ **Development of Effective Immunological Diagnostic Peptides**

Professor George Smith, CRC award recipient; Leslie Matthews

This research represents an altogether different approach. In brief, we plan to identify small peptides that specifically bind to antigens and antibodies associated with cancer. We call these "diagnostic" peptides because they should serve as diagnostic tests for cancer. Equally important, however, they might in the future provide a network of research paths for discovering unknown antigens. Such antigens could not only help to illuminate the disease process, but also serve as anti-cancer vaccine components.

The underlying supposition of the present research is that even diseases like cancer, which are neither infectious nor conspicuously autoimmune, may nevertheless be marked by the appearance, or a change in form or distribution, of disease-specific substances that we will call generically "neoantigens" (NeoAg's).

Tests for infectious diseases detect the infected subject's antibodies (Ab's) to pathogen antigens. Some autoimmune diseases are similarly diagnosed in part by detecting immunogenic. In using the term in this sense, we are abstracting somewhat from its original meaning; for we mean to include any disease-marking substance that can be specifically detected by a binding ligand, even if that detector molecule is not an antibody.

Bottom Line - The use of small peptides as antigen-antibody components, in place of large, natural, immunological components, should lead to earlier diagnosis and treatment that is more effective.

✍

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Ron Schmidt, Editor
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