There is no more exciting time to be a part of cancer medicine and prevention than now. We are now beginning to see the pay off from decades of dedicated work against cancer. Over the past three years, despite the growth and aging of our population, the total number of cancer deaths has declined for the first time.

Still, for far too many people, more than a million a year, cancer remains a very real threat to health, happiness,
and to life itself. And, when we consider how many of us have a family member or close friend with some form of cancer, it is clear that the collection of diseases we call cancer touches everyone.

So, while there is much we have accomplished, there is yet more we need to do. I truly believe, that with the continued support from the state and other donors, the Johns Hopkins Kimmel Cancer Center will shape the future that will ultimately see us conquer cancer.

WILLIAM G. NELSON, M.D., PH.D.
MARION I. KNOTT PROFESSOR AND DIRECTOR
THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER AT JOHNS HOPKINS
While cancer is now recognized as a genetic disease, investigators also realize that most of the gene mutations that lead to cancer are acquired, not inherited. As a result, this provides many opportunities for prevention through behavioral and environmental modifications to derail cancer initiation. Many of the most common cancers are caused by environmental and behavioral factors that are known and potentially alterable. Among these things are HPV infection, inflammation, poor diet, and smoking.
Collaborations with our many partners throughout Maryland have allowed us to educate our citizens about cancer prevention and detection. Our goal is not only to teach people about cancer screening services, but to guide and support them as they put what they’ve learned into place.

JOHN D. GROOPMAN, PH.D.
CHAIRMAN OF ENVIRONMENTAL HEALTH SCIENCES
JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH
Maryland has made great progress in combating its cancer problem. In less than 20 years, the state has dropped from third nationally in cancer incidence and death rates to 19th. We believe the state's involvement in cancer control through the Cigarette Restitution Fund program has played a key role in bringing down Maryland's rates.
### Johns Hopkins Has You Covered
Bringing the Best of Cancer Care to all Marylanders

<table>
<thead>
<tr>
<th>Year</th>
<th>Events</th>
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<tbody>
<tr>
<td>2003</td>
<td>Model for identification of carcinogens in food, dust, soil, and air developed. Partnerships with faith-based institutions in Baltimore City improve cancer education and screening. Microarray Core for biomarker discovered constructed. Preventive and therapeutic cervical cancer vaccine development begins. Marker for chronic inflammation used for colon cancer risk assessment. Risk-prediction algorithms augment colon cancer gene testing. Association between smoking and colon cancer studied. Spatial epidemiology used to quantify geographical variations in colon cancer incidence and pinpoint Maryland communities with environmental risks. Drugs that block the negative impact of smoke on cells are studied. Nr2f2 gene found to alter lungs' response to cigarette smoke. Hypermethylation is identified as an epigenetic marker of lung cancer. Influences of smoking cessation studied in girls 12-16. Researchers disprove association between SV40 exposure through polio vaccines and mesothelioma development. Antiangiogenesis drugs studied as a way to hold tumors in check. Combined approaches of cancer vaccines, chemotherapy and/or radiation therapy used to manage treatment resistance. Computerized technology helps identify cancer biomarkers and cancer-gene differences among races. Imaging technology used to monitor drug delivery response.</td>
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2004
- Molecular on/off switches engineered to change course of cancer cells.
- Landmark study begins to uncover causes of high cervical cancer rates among Maryland's African-American women.
- Internet, school-based counseling used in adolescent smoking cessation programs.
- Lung cancer therapeutics program launched.
- Clinical trials of therapeutic cervical cancer vaccine begin.
- Vehicle traffic in urban areas linked to concentrations of carcinogens in certain Maryland communities.
- HELP (Hopkins Early Lung Cancer Prevention Program) begins.
- Drugs that block tyrosine kinases, cancer cell accelerators, are studied for their ability to slow cancer growth.
- Arsenic-laced chicken manure found to be contaminating Maryland's Eastern Shore ground water.
- A molecular magnet called LigAmp pinpoints DNA mutations among thousands of cells and make it possible to detect microscopic cancer.

2005
- A novel approach called GIN I identifies gene mutations linked to prostate cancer.
- Smoking cessation methods in African-American men 18-24 are studied.
- Cost effectiveness and success of cancer control interventions and strategies evaluated.
- Nrf2 is target of lung cancer chemoprevention trials.
- Microarray technology used to uncover genetic changes in newborns caused by carcinogenic exposure through drinking water.
- Discoveries about the DNA repair process makes cancer cells more susceptible to radiation therapy.
- Exposures to secondhand smoke found to increase risk of cervical cancer.
- Statin-takers found to cut risk of advanced prostate cancer by half.
- Broccoli tea chemoprevention studies in breast, lung, prostate, and liver cancers begin.
- Free nicotine patches distributed in a joint smoking-cessation study between Johns Hopkins and the Washington County Health Department.
- Anti-inflammatory agents and dietary changes used in prostate cancer prevention studies.
- GSTP1 gene found to protect cells from cigarette smoke.
- Drug atrasentan slows progression and eases pain of prostate cancer.

2006
- Genetic blueprint for breast and colon cancer revealed.
- Kimmel Cancer Center called research powerhouse with five Center researchers named best in the field by Thomas Scientific. The investigators are the most frequently cited cancer researchers.
- SNP technology developed to rapidly pinpoint differences in the coding sequences of genes.
- Johns Hopkins Particulate Matter Research Group developed to study cancer risks of particulate matter air pollution.
- New therapy targets SRC gene in pancreatic cancer in an effort to extend survival.
- Blocking EGFR gene may improve outcome for esophageal cancer patients.
- Mathematical method for organized cancer gene discoveries developed.
- Bioinformatics method of cell signaling increases understanding of cancer and the signaling malfunctions that help it grow and spread.
- The first formal statistical translational clinical trial methodology is developed.
- Software created to make the complex mathematical package available to cancer centers throughout the country.
- Model developed to identify and quantify cancer drug synergies.
- Nurse-run smoking cessation program started.
- Chemical drug libraries purchased to screen for compounds that kill or inhibit tamoxifen-resistant breast cancer cells.
- Relationship between shortened chromosome ends, called telomeres, and increased development of prostate cancer in African-American men is studied.
The entire genetic blueprint for colon and breast cancers is deciphered.

HPV found to drive certain oral cancers and multiple oral sex partners determined most significant risk factor. The research is called one of the top cancer advances of 2007 by the American Society of Clinical Oncology.

Johns Hopkins team of CRF investigators selected by National Cancer Institute to map epigenetic changes related to cancer.

Geriatric Oncology Program established at Johns Hopkins Bayview to improve clinical research within the aging population most commonly affected by cancer.

Smokers in the Baltimore metro area provide DNA samples to help researchers pinpoint the genetic changes that cause some smokers to remain cancer free, while 10-20 percent of smokers develop lung cancer.

New data finds that an alteration of the EGFR gene results in poorer outcomes for patients with esophageal cancer. Clinical trials begin to test if adding drugs that block EGFR expression to standard chemotherapy and radiation improves survival.

Investigators devise means to sort out the accumulating genetic data linked to cancer. They develop a computerized, statistical method to mathematically decipher the significance of specific genetic alterations.

An inpatient nurse-delivered smoking cessation program tested in 150 patients as pilot for a standardized program in the state’s acute-care hospitals.

A pilot study of a panel of six genes is used to predict non-small cell lung cancer behavior.

A simple mouth rinse captures genetic signature for head and neck cancers and becomes prototype for inexpensive screening test for head and neck cancers.

A 3-D structure of the most commonly mutated cancer-promoting gene (oncogene) PIK3CA is created, providing a better understanding of how it is altered in colon, lung, breast, brain, stomach, and other cancers. Researchers work to develop mutation-specific inhibitors as new cancer therapies.

Pilot study is aimed at improving clinical trials patient accrual by pinpointing specific factors that mitigate participation.

A study of Maryland communities reveals environmental factors that contribute to cancer development.

Clinical trials begin of a new drug and other combined approaches to target and block expression of Bcl-2, a gene found to be over-expressed in most small cell lung cancers and linked to treatment resistance.

Patient navigators work with low-income, uninsured women in Baltimore City at high risk of developing breast cancer to facilitate education, screening, and treatment.
The Cigarette Restitution Fund: What is it?

WHAT IS IT? HOW MUCH MONEY DOES IT PROVIDE, AND WHERE DOES IT GO?

THE BASIC FACTS
In the late 1990s, attorneys from nearly every state in the U.S. brought suit against America’s cigarette manufacturers. They sought reimbursement for the huge costs to states incurred due to smoking-related diseases like cancer. Months of testimony, including evidence that the manufacturers had known for many decades the deadly and addictive nature of their product, were presented. In the end, the court ruled in favor of the states, slapping the nation’s major cigarette manufacturers with $53 billion in penalties. The award, known as the Master Settlement Agreement, was split between 46 states, including Maryland, five territories, and Washington, D.C.

In 1999, Maryland’s Governor Parris N. Glendening and the General Assembly were among the first of their lawsuit counterparts to use their award establishing the multi-million dollar Cigarette Restitution Fund (CRF). State leaders have continued to allocate funds throughout our state for smoking-cessation programs and education, crop conversion assistance for tobacco farmers, cancer research, prevention, education, screening, and treatment, and other smoking and cancer-related initiatives.

"There was certainly no shortage of possibilities on how to use these funds," said State Delegate Sandy Rosenberg. "We decided to establish the CRF because we felt it was important to use this settlement to affect some of the disturbing effects cigarette-smoking and cancer have had on the citizens of our state," he said.

SETTING THE BOUNDARIES
State leaders recognized one of the surest ways to impact cancer in our state was to look to Maryland’s two academic health centers—Johns Hopkins and the University of Maryland. In 2000, legislation was passed providing these institutions with grants for public health initiatives and cancer research.

Cancer Research Grant funds were restricted to seven cancers named in the law because of their high incidence and mortality rates in Maryland. The types of cancers funded included breast cancer, cervical cancer, colon cancer, lung cancer, melanoma skin cancer, oral cancer, and prostate cancer.

The CRF legislation required Hopkins to recruit and retain faculty and to assemble clinicians and researchers to conduct translational research of these cancers.

PUBLIC HEALTH GRANT
The CRF also provided Johns Hopkins a public health grant for the development of community-based cancer prevention, education, and screening programs. Hopkins clinicians collaborate with colleagues at University of Maryland, Sinai Hospital, the Baltimore City Health Department, and the Department of Health and Mental Hygiene. In 2009, Johns Hopkins, Sinai Hospital, and the Baltimore City Health Department added a colon cancer component.

The first Johns Hopkins project was a prostate-screening initiative launched in March 2001. The grant provided for prostate specific antigen (PSA) testing and digital rectal exams performed at designated community sites by Johns Hopkins physicians and nurses as well as any necessary follow-up care or treatment.

Funds were projected for subsequent years for public health programs addressing prostate and other targeted cancers.

THE CHALLENGE
With Maryland among the states leading the nation in cancer mortality, opportunities to make a difference through research and community screening abound. By the same token, it is the sheer complexity which make these endeavors onerous tasks. "Impacting the high cancer rates in Maryland is a great challenge," said John Groopman, Ph.D., chairman of environmental health sciences at the Johns Hopkins Bloomberg School of Public Health. He adds, "We have worked to find ways to reach out to our communities that have been suffering disproportionately from cancer. And, through research studies, we have begun to ferret out the biological, environmental, and behavioral factors that commingle to result in cancer."
By the Numbers

7 Targeted Cancers:
  Breast cancer
  Cervical cancer
  Colorectal cancer
  Lung cancer
  Melanoma skin cancer
  Oral cancer
  Prostate cancer

$2.25 million research dollars awarded
$1.2 million public health grant established
6 translational research awards made
6 faculty recruited
2001 RESEARCH AWARDS

IN JULY 2001, the first research grants under the CRF were funded. Fourteen, one-year grants were competitively funded. Of these first grants, six represented seed funding for young investigators that led to internationally-recognized, award-winning research advances. These discoveries, jump-started with CRF support, included a cervical cancer vaccine, the first comprehensive blueprints of the colon, breast, pancreatic and brain cancer genomes, the connection of HPV to a distinct subset of oral cancers and related risk factors, the identification of statins in prostate cancer prevention, pioneering work in the emerging field of epigenetics, and identification of a carcinogen-detoxifying gene pathway.

CERVICAL CANCER IMMUNITY
Cervical cancer has long been linked to the sexually transmitted human papillomavirus (HPV). HPV-associate cervical disease is three times the national average within Baltimore City's minority communities. Under the direction of researcher Connie Trimbile, M.D., a Cervical Diseases Center is established at Johns Hopkins to treat cervical dysplasia (the precursor to cervical cancer) and clinical studies of HPV-targeted interventions to stimulate immunity to HPV antigens and prevent the initiation of cervical cancer begin. ■

ACTIVE AND PASSIVE SMOKING AND CANCER INCIDENCE
Using the 30-year-old Washington County cohort study, a unique Johns Hopkins resource, investigators led by Anthony Alberg, Ph.D., estimated the effects of active and passive smoking on all cancer sites. Calculation of site-specific cancer incidence was done and the contributions of all sources of tobacco smoke will be estimated and reported. ■

NEW LUNG CANCER TARGETS
Julie Brahmer, M.D., and team are studying DNA obtained from lung sputum samples to identify tumor suppressor genes silenced by a genetic alteration known as hypermethylation. Researchers believe this alteration can be reversed with certain drugs reactivating the genes and their roles of suppressing tumor growth. Among the drugs being studied for their ability to "demethylate" suppressor genes are two natural products. ■

SMOKING AND LUNG CANCER
Construction of a cigarette smoke exposure facility for small animal exposure and validation of a mouse model for cigarette smoke-induced lung cancer is pointing to new avenues for lung cancer biomarker discovery and the preclinical trials of chemopreventive agents. Proteomics, which studies the expression, function, and interactions of proteins expressed by genes, is a new tool for discovery in cancer research. Shyam Biswal, Ph.D., led the first attempt to use proteomics in this mouse model to identify protein biomarkers associated with the onset of lung cancer after exposure to cigarette smoke. Biswal and team will identify proteins that may help in diagnostics, intervention, and risk assessment of cigarette smoke-associated lung cancer. Several chemopreventive agents will be evaluated. ■

BREAST CANCER-CAUSING PATHWAYS
While the BRCA1 and BRCA2 mutations provided key insights into the molecular genetic causes of breast cancer, they may be just one piece in a much larger puzzle. In epidemiological studies, 67 percent of families with four or five cases of early onset breast cancer could not be linked to these genes. Yin Yao, M.D., Ph.D., and team believe other genes work with BRCA2 to increase breast cancer risk and to control the age of onset and studied the BRCA2 pathway to identify other genetic culprits in breast cancer. ■

IMPROVING BREAST CANCER DETECTION
The ability of mammography to detect early breast cancer is reduced in younger women and women with dense breast tissue. Ductal lavage is a technique used to flush cells from the lining of breast cancer ducts, where breast cancer begins. The cells can then be examined to determine if cancerous cells are present, similar to a pap test for cervical cancer. It is not known yet how well this technique can pick up early cancers and if it is better than existing screening methods. It could be a powerful addition to available screening techniques, to improve early breast cancer detection rates, particularly among women at high risk for developing breast cancer. This study, led by Kathy Helzlsouer, M.D., M.H.S., took the first steps in determining the sensitivity and specificity of ductal lavage. ■

MOLECULAR SCREENING OF HEAD AND NECK CANCER
Scientists led by Joseph Califano, M.D., analyzed DNA of cells obtained from oral rinses and blood from 900 participants, including Caucasian, African American and Latino volunteers at high risk for head and neck cancer, to look for early genetic changes in the development of these cancers. Head and neck cancers can best be treated when caught in an early stage, but some of these cancers (those that occur at the base of the tongue, in the tonsils and larynx) are often caught in advanced stages. Molecular analysis, to look for subtle genetic changes in cells shed in saliva and blood, could lead to new prevention, diagnostic and treatment methods. ■

HPV'S ROLE IN ORAL CANCER
Tobacco and alcohol use are known to contribute to the development of oral cancers. Scientists hypothesize that the sexually transmitted human papillomavirus may augment these risks. Prior studies by Maura Gillison, M.D., Ph.D., suggested that HPV-positive head and neck cancers may comprise a distinct molecular, clinical, and pathologic disease very different from other types of the disease. They further explored the role of HPV in the initiation of certain oral cancers in the presence of the more traditional risk factors. ■

ANALYSIS OF THE COLORECTAL CANCER GENOME
Though a team of Johns Hopkins scientists,
including VICTOR VELCULESCU, M.D., PH.D., revealed cancer as a genetic disease caused by alterations in specific genes, many of these genes have yet to be identified. This is particularly true of colon cancer, where Johns Hopkins researchers were among the first to identify a series of genetic mutations associated with this disease. They continue this work with a genomewide analysis of colon and rectal cancer that identifies dozens of genetic changes in colon cancer, including those that may be prevalent among certain minority groups, revealing novel approaches to screening and diagnosis.

COLON CANCER BIOMARKER
The loss of imprinting of the IGF2 gene may be a genetic alteration common to colon cancer but not used as a potential biomarker for the disease. In a unique combined cancer genetics and epidemiological approach, researchers led by MARIA CRUZ-CORREA, M.D., are using tissue obtained in screening colonoscopies to characterize the role of loss imprinting of the IGF2 gene in colorectal cancer in Marylanders.

CADMIUM EXPOSURE AND PROSTATE CANCER RISK
Cadmium is one of the few environmental exposures linked to prostate cancer. Scientists, led by BRUCE J. TROCK, PH.D., suspect that this metal may generate damaging free radicals and displace beneficial zinc in prostate cells, potentially contributing to the development of cancer. They are testing this hypothesis in studies of cadmium, zinc, and selenium levels in prostate tissue samples from men known to work or reside in high cadmium exposure areas. This research also received funding in 2002.

QUIT SMOKING MESSAGES FOR TEENS
This project utilizes participatory research techniques to develop anti-smoking messages for females 12 years old to 16 years old. Investigators led by BARBARA CURBOW, PH.D., hope to determine how adolescent girls describe the process by which they have changed or prevented their smoking behavior and compare these reports to existing behavior and behavioral change theories. In addition, they will study how adolescent girls would urge other girls not to begin smoking or to quit smoking. The information will be used to develop and test anti-smoking messages.

BEHAVIOR AND CANCER RISK
While the causes of many cancers remain unclear, there are certain behaviors, including cigarette smoking, certain diets, environmental exposures, and alcohol use, that are known to increase cancer risk. ELIZABETH PLATZ, PH.D., is working with an 800,000-member, racially diverse and economically modest labor union to identify modifiable behaviors and environmental factors linked to breast, lung, prostate, and colon cancers. The first step in assembling the cohort is to identify a method of data collection that will yield the greatest and most reliable responses from the union members in Maryland. The racial diversity of the group in the Maryland locals may help uncover racial variations in cancer factors and lead to new interventions that could reduce statewide cancer risk.

CANCER GENE EXPRESSION ANALYSIS
QING-BIN GUO, PH.D., worked with gene microarrays, a new technology to evaluate thousands of genes simultaneously. The high-tech approach is expected to help target genes and other biomarkers for cancer detection, diagnosis, and treatment. This research also received funding in 2002.

NOVEL DRUG DEVELOPMENT FOR SOLID TUMORS
SAEED KHAN, PH.D., and team are working in the laboratory to synthesize bioactive molecules and create new anticancer drugs to treat prostate, breast and colon cancers. These new compounds are being designed to be selectively toxic to cancer cells, particularly at metastatic sites now resistant to standard therapies, while sparing normal cells from damage. The project will provide critical capacity for small molecule drug development at our institution.

CANCER EDUCATION FOR KOREAN AMERICAN WOMEN
Cancer is a leading cause of death among Korean women age 24 to 64. Breast and cervical cancers are among the most commonly diagnosed cancers in Korean American women. These women have low usage of mammography and pap tests because they lack knowledge of screening and have limited access to these cancer-screening methods. Clinician-scientists, directed by KEE-SOON JUON, PH.D., are working with local Korean churches to develop culturally sensitive materials to educate women and enroll them in screening programs in an effort to impact cancer death rates.

CANCER-CAUSING AGENTS IN THE MARYLAND ENVIRONMENT
Cancer is an important public health concern in Maryland and Baltimore City. The state and city consistently have some of the highest rates in the nation. Based on ambient air toxic levels, Baltimore City and M. aryland are ranked as first and third in the nation for cancer mortality. Exposure to many important environmental carcinogens, such as pesticides, polycyclic aromatic hydrocarbons, and volatile organic compounds, can occur in combination and from multiple-media (air, water, diet, dust, soil) and through multiple routes (ingestion, inhalation, and absorption through the skin). TIMOTHY J. BUCKLEY, PH.D., and THOMAS BURKE, PH.D., are identifying and prioritizing environmental carcinogens in Maryland, based on the potential for exposure and risk. This work will provide focus and definition for future efforts to study cancer epidemiology and prevention.
Cervical Cancer
CRF INVESTIGATOR: CONNIE TRIMBLE

RESEARCH
Cervical cancer is caused by human papillomavirus (HPV) infection. Precancerous lesions occur years before cancer and are easily detectable through pap smears. Still, cancer rates among women in Baltimore City and Maryland's Eastern Shore are three times the national average.

TRANSLATION
Researchers work to develop a vaccine that causes immune cells to recognize and attack HPV and clear it out. Without the virus, the cancer cannot survive.

APPLICATION
With one shot in each arm, a 44-year-old woman, becomes the first patient to receive Johns Hopkins-developed therapeutic HPV vaccine for cervical cancer. Many patients have since been treated, and based on early promising research, phase II trials are scheduled to begin in winter 2009.
Over $2.1 million was received from the Cigarette Restitution Fund awards totaling in Maryland. The most common and interventional cancers in lung, breast, cervical, skin, colon, oral, and prostate cancers, which are among the most common and deadly cancers in Maryland. Restitution Fund (CRF), Johns Hopkins directed its efforts to translational research in lung, breast, cervical, skin, colon, oral and prostate cancer, which are among the most common and deadly cancers in Maryland. With money from the Cigarette Restitution Fund (CRF), Johns Hopkins directed its efforts to community-focused research in lung, breast, cervical, skin, colon, oral and prostate cancer, which are among the most common and deadly cancers in Maryland.

“We are taking aggressive action to close the book on Maryland’s tobacco heritage and improving the health and quality of life for all Marylanders,”said Governor Parris N. Glendening in 2001. “We have created programs to help farmers stop growing tobacco, we have passed laws to help protect people from second-hand smoke and we have sponsored educational and research programs across the State to find out why we have such a high cancer rate in Maryland. Projects like this one at Johns Hopkins will help us root out the causes behind this and allow us to find ways to lower both the cancer rate and the impact it has on our community.” Baltimore City currently leads the state and nation in deaths due to cancer-related air pollutants and prostate cancer. Maryland consistently ranks high in deaths due to cancer-related air pollutants and prostate cancer. Oral swabs for head and neck cancers; Pap smears for cervical cancer; mammography for breast cancer were done through other research grants.

“If my mother had regular screening for breast cancer, she might be alive today,” says Sandra Briggs, Executive Director of Bea Gaddy’s Family Centers, Inc. and daughter of community activist and city council member Bea Gaddy, who had recently died of breast cancer and for whom one of the Centers is named.

Maryland Uses Big Tobacco Money to Beat Cancer

CRF Making Headlines in 2001

Cancer, a disease attacking Baltimoreans at an alarming rate, costs the lives of more than 10,000 Marylanders each year. Screening tests that can provide early detection and cure are vastly underused by minorities and the poor who suffer disproportionately from prostate, breast, oral, and cervical cancers. Now through the Maryland Department of Health and Mental Hygiene Cigarette Restitution Fund Program, Johns Hopkins and the Baltimore City Health Department and Sinai Hospital, are working together to bring cancer screening into these communities. Officials are setting up sites in Baltimore City community health centers to offer simple screening tests and provide information that could save lives.

The screening program was kicked off on November 13, 2001, at the Park Heights Community Health Alliance. Secretary of Health, Dr. George Benjamin, members of the Maryland General Assembly representing Baltimore City, then-Baltimore City Mayor Martin O’Malley, City Council Members, and other community leaders were invited to help promote the event. Other community sites included the Urban Medial Institute, UniversityCare at Edmondson Village, Bea Gaddy’s Cancer Education and Prevention Center, the Hispanic Apostolate, Garden of Prayer Baptist Church, the Korean Resource Center, the Baltimore City Health Department Oral Health Services Program and Morgan State University.

With money from the Cigarette Restitution Fund (CRF), Johns Hopkins directed its efforts to translational research in lung, breast, cervical, skin, colon, oral and prostate cancer, which are among the most common and deadly cancers in Maryland. Nineteen scientists at Johns Hopkins received the first CRF awards totaling over $2.1 million.

CRF Investigators Receiving Honors and Awards

Martin Abeloff, M.D., was among the top cancer physicians listed by Good Housekeeping magazine. Oncologists were nominated by department chairs and section chiefs in surgical, medical, and radiation oncology at major medical centers throughout the country.

Joseph Califano, M.D., and Maura Gillison, M.D., Ph.D., were among only five physicians worldwide to receive an investigator award from the cancer Research Fund of the Damon Runyon-Walter Winchell Foundation sponsored by Eli Lilly and Company. Gillison was chosen for her clinical studies associating the human papillomavirus with head and neck cancers. Her mentor, Keetly V. Shaha, M.D., also received an award. Califano was selected for research in head and neck cancers as well.

Time magazine named David Sidransky, M.D., in its special issue “America’s Best Science and Medicine.” Sidransky was recognized for his work using subtle genetic alterations to develop early screening tests for a variety of cancers, including bladder, colon, head and neck, and lung cancers.

Victor Velculescu, M.D., Ph.D., received the American Pharmacists Association and Science Prize for Young Scientists for his work in developing SAGE, a method to rapidly identify disease-related genes and measure gene expression.
In 1993, Lloyd Bowser had lost 63 pounds and was feeling generally lousy. Among the tests his doctor performed to determine the cause of his weight loss and ill health was a prostate specific antigen test (PSA). Lloyd admits he had never had his PSA checked before and really wasn’t clear on its purpose. When the results came back though, he learned that his PSA was 32.

“I may not have known what a PSA was, but I had a feeling 32 was bad,” says Lloyd. In fact, he was correct, with 0-4 being the normal range for PSA, his doctors’ knew immediately what was likely wrong with Lloyd—prostate cancer.

Lloyd, like many African American men in Baltimore City, was unaware that regular physical examinations and a simple blood test that identifies rising levels of antigens produced by abnormal cells in the prostate, can detect the cancer in an early and curable stage. Lack of regular screening is one reason that Baltimore City leads the nation in prostate cancer incidence and deaths.
2002

By the Numbers

7 CRF Targeted Cancers:
- Breast cancer
- Cervical cancer
- Colorectal cancer
- Lung cancer
- Melanoma skin cancer
- Oral cancer
- Prostate cancer

Research:
- $3 million research dollars awarded
- 8 faculty members recruited
- 5 faculty retained
- 12 translational research awards

Prostate Cancer Prevention, Education, Screening and Treatment
- $1.4 million public health grant awarded
- 405 people educated
- 331 people screened
- 4 men diagnosed and treated for prostate cancer

Making the Connection: Research ➔ Translation ➔ Application
Breast cancers often respond well to drug therapy but, over time, become resistant. Ben Ho Park, M.D., Ph.D., and team introduced specific known gene mutations into breast cancer cell lines to see how the mutations help cancer cells resist chemotherapy. The team envisions a library of cell lines to allow development of multiple drugs that target different pathways and prevent the emergence of resistant cancer cells. In 2004, Park continued his CRF research identifying novel compounds that target tamoxifen-resistant breast cancer. ■

FINDING A RED FLAG FOR BREAST CANCER

Women with proliferative benign breast disease have an increased risk of breast cancer. In order to implement effective preventive strategies, it is necessary to identify which women will go on to develop breast cancer and to distinguish those cancers that will be noninvasive and manageable and those that will become invasive and difficult to treat. The goal of a study by Kala Visvanathan, M.H.S., M.D., is to find specific biomarkers that would make it possible to select out women with proliferative or noninvasive cancer who are at risk of developing invasive breast cancer. These markers would be used in the clinic as targets for chemopreventive agents. This research also received CRF funding in 2003. ■

A BREAST CANCER VACCINE

A study by Leisha Emens, M.D., Ph.D., focused on an immune-system boosting vaccine used in combination with timed sequential doses of chemotherapy. Advanced breast cancer is often attributed to the failure of post-surgical therapies to destroy all remaining cancer cells. These resistant cells ultimately result in metastatic disease with very poor cure rates. Activating the immune system with anti-tumor vaccines represents a promising approach to overcoming drug resistance and driving the immune system to eradicate resistant tumor cells. The researchers believe integrating the vaccine approach with traditional chemotherapy and/or radiation therapy can work in synergy to destroy tumor cells. ■

UNCOVERING CANCER TARGETS

Investigating the relationship between subtle DNA changes, known as polymorphisms, and cancer could help identify new biomarkers for early detection as well as potential targets for drug therapy. Ingo Ruczinski, Ph.D., and team developed a sophisticated computerized technology for analyzing data to uncover such relationships. It will also reveal genetic cancer-related differences that may exist between races, helping to uncover the cause of high cancer rates among certain minority groups. ■

HEAD AND NECK CANCER RESOURCE

Head and neck cancers, and particularly oral cancers, are among the most devastating cancers affecting Marylanders. Significant basic and clinical research has been conducted independently at Johns Hopkins and the University of Maryland and could be accelerated with joint research endeavors. Collaborations already under way include studies of molecular genetic detection of head and neck cancer in saliva and tissue, the association between the human papilloma virus (HPV) and head and neck cancer, and genetic culprits in oral cancers. Maura Gillison, M.D., Ph.D., proposes additional projects including studies in rarer populations affected by head and neck cancers, such as non-smokers and non-drinkers, that would essentially be impossible to complete without collaboration between institutions. The ability to double the number of patients studied and share resources, such as tissue samples, data, and biostatistical information, is expected to lead to more rapid discoveries and advances in the treatment of head and neck cancers. ■

TARGETED THERAPIES FOR PROSTATE CANCER

Cellular biology advances have revealed an expanding number of genetic abnormalities unique to cancer cells and believed to be involved in the development, growth, and spread of tumors. Researchers are now studying several drugs, known as target compounds, that specifically focus on these abnormalities. Rather than destroying tumors, these new compounds appear to halt cancer growth and prevent them from spreading and invading healthy tissue and organs. Investigators, led by Michael Carducci, M.D., began studies of these targeted compounds in animal and tumor models using sophisticated imaging technology to monitor drug delivery to tumors and changes in tumor size. Clinical trials for...
prostate cancer were proposed in collaboration with Howard University and the community centers participating in the CRF Baltimore City Cancer Plan. This research also received CRF funding in 2004.

TACKLING PROSTATE CANCER IN AFRICAN AMERICAN MEN

African American men who develop prostate cancer are generally younger than white counterparts, have more extensive disease, and a higher incidence of related bone pain. In addition, mortality rates among African Americans are three times greater than those of white men. These observations, coupled with the increasing nature of the disease, underscore the need for novel therapies to reduce the incidence and death rates from prostate cancer, particularly among African American men. This study, led by CHARLES DRANE, M.D., PH.D., used new therapies that manipulate the immune system to generate a response against evolving prostate tumors as well as a combined vaccine/chemotherapy approach in hopes of identifying new, curable therapies for an often untreated tumor. This research also received CRF funding in 2003.

CULTURAL ANTI-SMOKING PROGRAM

While much progress has been made among Americans overall in smoking cessation, Korean Americans, particularly men, continue to have high rates of smoking and smoking-related diseases, including lung cancer. Language and cultural barriers often impede the usefulness of established anti-smoking programs among this group. Working with the Korean Resource Center, MIYONG T. KIM, R.N., PH.D., and team utilized Korean health care providers, churches, social clubs, and news media to develop and implement a culturally sensitive smoking cessation program to decrease smoking rates and smoking-related cancer occurrence and death in this population.

ATTACKING METASTATIC CANCERS

Research by SAEED KAHN, PH.D., and team focused on the development of new agents to target metastatic prostate, colon, and breast cancers. Among those already in development is a prostate specific antigen (PSA)-based pro-drug therapy that involves the administration of inactive drugs that become turned on and activated against cells with increased PSA activity. Similar agents are in development for colon and breast cancers.

CANCER OUTREACH

JANICE V. BOWIE, PH.D., M.P.H., builds upon 25 years of experience with community-focused intervention activities targeting breast cancer, cervical cancer, and prostate cancer among African Americans. She fostered partnerships with faith-based institutions to design culturally-relevant cancer prevention and control educational materials and programs. The unique approach not only defined the basis of health disparities in cancer but promoted mechanisms for implementing and sustaining changes.

HPV VACCINE

The causative role of the sexually transmitted Human Papillomavirus (HPV) has been well established in cervical cancer. Researchers, including RICHARD B. RODEN, PH.D., worked to develop a single vaccine aimed at elimination of the 15 or more types of cancer-causing HPV, and, as a result, cervical cancer.

INFLAMMATION AND THE RISK OF COLON CANCER

Data from epidemiological studies and clinical trials suggest that chronic inflammation may play an important role in the development of colon cancer, but the precise nature of this risk is still unknown. Hopkins researchers, including THOMAS P. ERLINGER, PH.D., believe that simple, commonly measured markers of inflammation may be the key to identifying healthy persons at risk for developing colon cancer. They evaluated the relationship between modest elevations of C-reactive protein and interleukin 6 in a cohort study of a group of people living in Washington County, Maryland. This research also received CRF funding in 2003.

THE MATHEMATICS OF CANCER RISK PREDICTION

In recent years, important discoveries about the genes that cause colon cancer have led to the development of genetic tests for cancer-related biomarkers specific to the disease, identifying and counseling individuals at high risk for colon cancer because of their family history is increasingly common but quite complex. As a result, Hopkins investigators, led by JEANNE KOWALSKI, PH.D., G. STEVEN BOVA, M.D., and GIOVANNI PARMIGIANI, PH.D., are incorporating these advances into risk prediction algorithms that use laboratory-based biological knowledge about susceptibility genes to improve screening, prevention, and genetic testing and to design health behavior interventions, cancer prevention studies, and genetic epidemiology studies. This research also received CRF funding in 2003, 2003, and 2006.

CONNECTING SMOKING AND COLON CANCER

Cigarette smoking has been associated with a number of cancers, but when it comes to the relationship between smoking and colon cancer, there is no clear scientific consensus. ELIZABETH PLATZ, Sc.D., M.P.H., believes that carcinogens in cigarette smoke act early in the carcinogenic pathway from normal colon cells to colon cancer. Platz and colleagues examined whether smoking influences the development of pre-cancers for colorectal cancer called adenomatous polyps. The investigators also studied common alterations in genes, known as polymorphisms, that affect cell cycle control to learn if they play a role in the development of colorectal adenomas.
THE GEOGRAPHY OF COLON CANCER
Research by Xuguang (Grant) Tao, M.D., Ph.D., uses the emerging discipline of Spatial Epidemiology to describe, quantify, and explain geographical variations in colon cancer incidence. Maryland ranks third in the nation in deaths due to colon cancer. Aided by Geographic Information System (GIS) technology, which provides widespread availability of environment pollution related electronic databases, cancer registry systems, and powerful computer systems, the investigators hope to identify Maryland communities or populations that may have high environmental risks for colon cancer. This research also received CRF funding in 2003.

LUNG CANCER DNA
Lung cancer develops over time through the progression of precancerous lesions in lung airways. Cells in these abnormal regions harbor many of the DNA changes that lead to lung cancer, and early detection of these abnormalities provides one of the best hopes for instituting preventative measures. Researchers Stephen G. Baylin, M.D., and James G. Herman, M.D., played a key role in identifying one of these DNA changes known as altered DNA methylation. They are now developing novel measures to monitor risk, institute prevention strategies, and identify early detection methods for lung cancer. DNA assays will be used to identify biomarkers, such as altered methylation, that predict lung cancer occurrence in high-risk individuals and to monitor the effectiveness of chemoprevention strategies. New prevention strategies that target specific DNA abnormalities in lung cancer will also be tried.

SOLVING A CANCER MYSTERY
Simian Virus 40 (SV40) naturally infects macaque species of monkeys in Asia, and though there is no known reservoir of SV40 in the U.S., tens of millions of U.S. residents were potentially exposed to the virus when many polio vaccines were inadvertently contaminated with the virus between 1955 and 1963. The strongest cancer association for SV40 is in mesothelioma, a malignancy of the lining or epithelium of the lungs. Some studies indicate that asbestos exposure and SV40 are cofactors working together in causing the development of mesothelioma. Still others have found no evidence of SV40 in mesothelioma tissue. Johns Hopkins researchers Keerti V. Shah, M.D., and Stephen C. Yang, M.D., resolved the controversy through a detailed examination of the tumor cell-virus relationship in studies of patients with active mesothelioma for evidence of SV40 infection and other risk factors.

DECIPHERING PROSTATE CANCER DISPARITIES IN MARYLAND
Prostate cancer is the major cause of cancer death in Maryland, with rates disproportionately higher than the rest of the nation, particularly among the African American population. Researchers led by Elizabeth Platz, Sc.D., M.P.H., conducted a series of interrelated research and service projects focused on improving the outcomes of prostate cancer in Maryland, and particularly Baltimore City. The program includes projects examining issues in prostate cancer screening, a correlational study of the relation of environmental factors related to prostate cancer, and population-based etiologic, behavioral, and intervention studies.

SMOKING MESSAGES FOR AN INTERNET SOCIETY
Investigators led by Dina Borzekowski, Ed.D., examined how the Internet can play an effective role in reducing adolescent smoking, and, in the long run, reduce the prevalence of smoking-related cancers in Maryland. Researchers will study how Maryland adolescents evaluate Web sites that convey smoking prevention and cessation messages and use the findings to enhance anti-smoking and prevention messages via the Internet. A seminar offering practical recommendations to the Maryland Department of Health and Mental Hygiene Office of Health Promotion, Education and Tobacco Use Prevention was offered so that health staff and organizations throughout the state would be better advised in the creation of effective smoking prevention Web sites. This research also received CRF funding in 2003.

CUTTING OFF THE BLOOD SUPPLY TO TUMORS
Tumor angiogenesis, or the recruitment of new blood vessels by tumors, is a process which tumors require for continued growth. Therapies targeting new blood vessel formation represent a promising strategy in blocking tumor growth and spread. Kimmel Cancer Center scientists led by Roberto Pili, M.D., combined laboratory and clinical research to develop new drugs combining angiogenesis inhibitors, cell differentiation-inducing agents, immune system modulators, and cytotoxic, or cell destroying, compounds for prostate cancer treatment. Using expertise in new drug development and a pre-clinical understanding of tumor angiogenesis, the investigators developed molecular targeted therapies to control solid tumor growth. This research also received CRF funding in 2001.
NEW PROSTATE CANCER GENE IDENTIFIED
Researchers identified a new genetic culprit—dietary implications—in the initiation of prostate cancer. Investigators found the AMACR gene to be overexpressed by as much as nine times in prostate cancer and a prostate cancer precursor known as prostatic intraepithelial neoplasia (PIN). “This gene appears to play an important role in the oxidation or metabolism of fatty acid molecules such as those found in dairy products and beef,” said CRF investigator ANGELO DEMARZO, M.D., PH.D., of the findings reported in Cancer Research. “AMACR could serve as an excellent early marker for prostate cancer and could also help in the development of prevention methods.”

A SERVING OF BROCCOLI A DAY COULD KEEP THE ONCOLOGIST AWAY
Johns Hopkins researchers who formerly identified a compound in broccoli and other vegetables believed to prevent cancer, have now figured out how it works. Scientists from the Johns Hopkins Bloomberg School of Public Health have identified the specific genes and enzymes involved in this naturally-occurring cancer prevention mechanism.

They have developed a blueprint mapping the specific genes, and the enzymes they produce, that enable the compound sulforaphane present in broccoli to remove toxins from cells and prevent cancer. “Carcinogens mutate the DNA in genes, which leads to cancer. Now, we know sulforaphane present in broccoli can affect an extensive network of genes and pathways and rid the body of carcinogens,” says SHYAM BISWAL, PH.D., of the discovery, funded in part by the Maryland Cigarette Restitution Fund, was made using new “gene chip” technology that allows researchers to monitor the complex interactions of thousands of proteins within the entire genome. This first-ever gene profile of a cancer-preventing agent provides a new understanding of the body’s defense mechanisms and could lead investigators to other food compounds and strategies for cancer prevention.

ONCE THOUGHT TO CAUSE CANCER, THE PILL IS FOUND TO PREVENT IT
A new study conclusively reverses the long-held notion that birth control pills increase a women’s risk for breast cancer. In a New England Journal of Medicine editorial published June, Johns Hopkins Kimmel Cancer Center breast cancer experts say results form a study of more than 10,000 women nationwide confirms that taking birth control pills does not lead to breast cancer, and, in fact, decreases their risk of developing endometrial and ovarian cancers. Results of the Women’s Contraceptive and Reproductive Experiences (Women’s CARE) study, which included both white and African American women, prove, with 95 percent certainty, that there is no link between taking birth control pills and breast cancer risk. “Now, what we need to focus on developing an oral contraceptive that helps reduce the risk of breast cancer while preserving its current cancer preventive qualities,” says KATHY HELZLSOUER, M.D., M.H.S., professor of epidemiology and oncology and CRF-sponsored investigator.

STOOL TEST FOR COLON CANCER
Scientists at the Johns Hopkins Kimmel Cancer Center have developed a safe and reliable stool test that can detect the earliest, curable stages of colon cancer. Early studies of the test, which uses a newly developed technology to detect and highlight a key genetic marker of the disease, were reported in the January 31, 2002, issue of the New England Journal of Medicine, and are the culmination of more than a decade of effort to uncover disease mutations and apply them to screening and early detection.

The investigators used the test on stool samples collected from 74 individuals. The test detected a telltale genetic mutation in 61 percent of those with early colon cancer, in half of those with premalignant polyps known as adenomas and in none of those who were disease free. These findings demonstrate that the test reliably detects cancers at an early and curable stage, and that it yielded no false positives.

“We still have a way to go before we can confidently use such a screening test in the general population, but we are encouraged by the fact that we’ve detected mutations in a significant fraction of the patients with early stage tumors and never in people free of disease,” says Bert Vogelstein M.D., professor of oncology at the Kimmel Cancer Center and leading colon cancer expert.

The investigators expect it will take an additional three to five years before the test will be available clinically. Colorectal cancer is one of seven cancers targeted by the Maryland Cigarette Restitution fund cancer initiatives. VICTOR VELCULESCU, M.D., PH.D., a researcher in Dr. Vogelstein’s laboratory, has received a CRF grant to conduct a mutational analysis of the colon.

BEA GADDY CANCER PREVENTION AND EDUCATION CENTER OPENS
State Senator Nathaniel McFadden and Sandra Briggs, daughter of Bea Gaddy, “the Mother Teresa of Baltimore,” cut the ribbon for the opening of the Bea Gaddy Cancer Prevention and Education Center in June 2001. The center is among the community partners working with Johns Hopkins in its CRF cancer screening and education outreach. Since the opening, Briggs reports an ongoing stream of visitors participating in breast, oral, and prostate cancer screenings and obtaining information. “One day, we had 140 people come through in just two hours,” she says. “Now clearly that demonstrates both the interest and need for such programs in our community.”

“On day, we had 140 people come through in just two hours. Now clearly that demonstrates both the interest and need for such programs in our community.”
TIMELINE OF DISCOVERY

HPV and Oral Cancers

CRF INVESTIGATOR: MAURA GILLISON

2001
Conducts the first detailed research of the relationship between HPV and head and neck cancers and proves that HPV is a cause of certain oral cancers.

2002
Identifies HPV + head and neck cancer as a distinct molecular, clinical, and pathological disease associated with improved survival.

Begins study of 100 tonsillar cancer patients and health controls, collecting blood samples and examining a variety of behaviors, including smoking, drinking, family history, poor oral hygiene, multiple oral sex partners, and other sexual behaviors that would increase the potential for HPV exposure.

2003
Begins risk-assessment study of an oral “Pap smear” or oral swab to see if oral infection with HPV can be detected before cancer develops.

2004-2005
Launches three-pronged attack against oral cancers, conducting research on exposures that lead to HPV infection, new methods of detecting infection, and a therapeutic vaccine.

2006
Clinical trials of a therapeutic vaccine for head and neck cancers begin.

2007
Findings reported in the New England Journal of Medicine show that HPV drives tonsillar cancers and identifies multiple oral sex partners as the overriding risk factor for the disease, superseding any other risk factors, including drinking and smoking.

The American Society of Clinical Oncology, the world’s leading organization of clinical cancer specialists, names Gillison’s HPV and oral cancer research one of the top cancer advances of 2007.

2008
Identifies HPV infection as the underlying cause of approximately 20,000 of these cancers and calls for a broader use of HPV vaccines in a Centers for Disease Control and Prevention (CDC) report, believed to be the first and most comprehensive assessment of HPV-associated cancer data in the United States.

Gillison finds that simple “swish and spit” oral rinses can successfully track oral HPV infection over time, opening the door to a potential non-invasive screening test to detect the disease and monitor for tumor recurrence.

PROGRESS AGAINST HPV-ASSOCIATED CANCERS

RESEARCH
Oral cancers have been steadily on the rise since 1973. While the human papillomavirus (HPV) had been detected in these cancers for sometime, its role remained unclear.

TRANSLATION
Gillison was the first to prove HPV as the cause of certain oral cancers. In addition, she found the HPV cancers were a distinct subtype of oral cancer which had higher survival rates. Further research revealed multiple oral sex partners as the overriding risk factor for the disease.

APPLICATION
Gillison finds that currently available HPV vaccines used to prevent cervical cancer have the potential to reduce the rates of other HPV-associated cancers, like oral cancers. Broader use of the vaccines, currently given only to girls and young women, could impact HPV related cancer rates among both men and women.
Based on the success of the community outreach undertaken with the CRF public health grant, The Johns Hopkins Cancer Health Disparities Research Program earned a multimillion dollar award to augment these efforts. “Cancer screening and treatment services are readily available, but there are barriers to accessing this care that we need to address in minority populations,” says Jean Ford, M.D. As director of the CRF Public Health Grant, Ford collaborates with a coalition of Baltimore hospitals and local organizations in providing medically underserved populations with services for prostate cancer. He has leveraged this work and earned additional funding to provide similar services for breast cancer and colon cancer.
By the Numbers

7 Targeted Cancers:
- Breast cancer
- Cervical cancer
- Colorectal cancer
- Lung cancer
- Melanoma skin cancer
- Oral cancer
- Prostate cancer

Research:
- $3 million research dollars awarded
- 9 faculty recruited
- 2 faculty retained
- 9 translational research awards

Prostate Cancer Prevention, Education, Screening and Treatment:
- $1.4 million public health grant awarded
- 159,619 people reached through media
- 18,391 people educated
- 234 cancer screenings
- 2 men diagnosed and treated for prostate cancer
CLEANING UP MARYLAND TO PREVENT CANCER

Maryland’s cancer death rates are among the highest in the nation. Maryland ranked third in a report by the U.S. Environmental Protection Agency on “estimated cancer risk due to air toxic ambient concentrations,” and Baltimore City ranked first for “added cancer deaths attributable to air toxics.”

Investigators TIMOTHY BUCKLEY, PH.D., M.H.S., and THOMAS A. BURKE, PH.D. believe human exposure to cancer causing agents in the environment is a contributing factor to Baltimore City’s and the State’s overall higher cancer rates.

Epidemiological studies have shown that living in areas that are closer to sources of air pollution is related to an increased risk of lung cancer. Others have shown that urban populations have higher incidence rates for a majority of cancers. By evaluating both the geographical distribution of environmental carcinogens and cancer mortality rates for Maryland, insights can be gained regarding at-risk populations and effective prevention strategies. Investigators are not only looking at air, but food, dust, soil, and other environmental media with which chemical carcinogens come in contact. While the inhalation of carcinogens is most commonly thought of, the consumption of them in food and absorption through skin represent exposures that far exceed inhalation.

This study characterized exposure and risk in urban areas of Maryland, identified biomarkers to evaluate exposure and risk for Marylanders, identified the most vulnerable populations within the State, and generated data for targeted prevention and intervention strategies for cancer reduction in Maryland.

BREATHING EASIER IN BALTIMORE

TIMOTHY BUCKLEY, PH.D., stood on city streets and collected bus emissions to evaluate the health effects of citizens breathing daily doses of these carcinogenic fumes. “Assessing a community’s cancer risk could be as simple as counting the number of buses, trucks and cars that pass through the neighborhood,” said Buckley. One result of the team’s research was the development of the Clean Fuel Buses group and its booklet “Breathing Easier in Baltimore.” The booklet contains Buckley’s research results and is being used to influence the Mass Transit Administration to examine its policies for the type of fuel it uses and the types of buses purchased in the future.

SMOKING AND LUNG CANCER

Construction of a cigarette smoke exposure facility by SHYAM BISWAL, PH.D., was funded under a previous CRF grant and is now being used in animal trials to measure cancer-causing particles, including carbon dioxide, nicotine, and acrolein. These animal models are revealing new information about smoking-related carcinogens and the cellular changes that ultimately result in lung cancer. This work has been published in two scientific journals and was reported at the Society of Toxicology annual meeting in March 2002. The investigators are now expanding their research to identify and test chemopreventive agents that could block the negative impact of cigarette smoke on cells, or specific cellular changes that could serve as biomarkers for the early detection of lung cancer.

While the inhalation of carcinogens is most commonly thought of, the consumption of them in food and absorption through skin represent exposures that far exceed inhalation.
"CUT AND PASTE" GENE TECHNOLOGY CREATES A MOLECULAR SWITCH

Using a technique called domain insertion, MARK OSTERMEIER, PH.D., used enzymes as molecular scissors to cut and paste different genes into a single gene strip. The end result was a molecular "switch"—a microscopic protein partnership in which one member controls the activity of another. One part of the coupled gene sends a signal telling the other part to change its behavior. Ostermeier said one part of the fused gene might only react to cancer cells and signal its partner to release a toxin to kill diseased tissue but leave healthy cells alone.

LUNG CANCER THERAPEUTICS PROGRAM

A multidisciplinary team of clinical, basic, and population scientists, led by JULIE BRAHMER, M.D., JAMES HERMAN, M.D., PH.D., and REX YUNG, M.D., developed the Lung Cancer Therapeutics Program to develop better lung cancer prevention and treatment options and to build stronger connections between laboratory and patient-based research. The investigators used laboratory findings about the initiation and progression of lung cancer to develop clinical trials for risk assessment and early detection of lung cancer. This work will complement the Johns Hopkins Lung Cancer SPORE (Specialized Programs of Research Excellence), quickly moving laboratory discoveries to cancer treatments.

BREAKING DOWN BARRIERS

The burden of cancer is not shared equally by all populations. Much evidence points to broad disparities in cancer prevention, treatment, health service utilization, and health outcomes across racial/ethnic and socio-economic groups in the United States. But while many experts have offered explanations for these health disparities, they have not suggested interventions to cost-effectively reduce them.

A team led by CHRIS GIBBONS, M.D., M.P.H. developed community-based health risk management to administer health risk assessments, conduct motivational interviews, provide culturally appropriate translation of current health guidelines, provide lifestyle counseling, coordinate insurance, and facilitate medical care and prevention services to improve adherence to recommended screening and early diagnosis guidelines and follow-up support.

IN OTHER RESEARCH

The Avon Foundation joined the Johns Hopkins Kimmel Cancer Center and its community partners to further improve breast cancer care for the women of Baltimore City. The Avon Access to Breast Health Initiative will provide funding for education and screening services currently provided through Hopkins partnerships with community-based cancer education centers developed through the CRF-sponsored Baltimore City Cancer Plan. “We are honored to count Avon among our partners in reducing the high cancer rates in our community,” says JEAN FORD, M.D., director of the CRF’s public health grant. This gift also supported construction of the Avon Breast Center and breast cancer treatment at Hopkins. The new initiative will reach women and add to services currently provided through Hopkins partnerships with community-based cancer education centers developed through the CRF-sponsored Baltimore City Cancer Plan. “We are honored to count Avon among our partners in reducing the high cancer rates in our community,” says JEAN FORD, M.D., director of the CRF’s public health grant. This gift provides an opportunity to reduce the burden of breast cancer in underserved communities. “It is our goal to attract similarly generous contributions to reduce the burden of other cancers that show racial and geographic disparities, including prostate, oral, cervical, and colon cancers,” he says. ■

AVON ACCESS TO BREAST HEALTH CARE INITIATIVE
The Avon Foundation joined the Johns Hopkins Kimmel Cancer Center and its community partners to further improve breast cancer care for the women of Baltimore City. The Avon Access to Breast Health Care Initiative will provide funding for education and screening services currently provided to underserved minority and low-income women in Baltimore City. The Avon Access to Breast Health Care Initiative was funded through a $10 million gift made by the Avon Foundation to the Kimmel Cancer Center. It is the largest single gift ever to the Johns Hopkins Breast Cancer Program. In addition to the Breast Health Initiative, the gift also supported construction of the Avon Breast Center and breast cancer research at Hopkins. The new initiative will reach women and add to services currently provided through Hopkins partnerships with community-based cancer education centers developed through the CRF-sponsored Baltimore City Cancer Plan. “We are honored to count Avon among our partners in reducing the high cancer rates in our community,” says JEAN FORD, M.D., director of the CRF’s public health grant. This gift provides an opportunity to reduce the burden of breast cancer in underserved communities. “It is our goal to attract similarly generous contributions to reduce the burden of other cancers that show racial and geographic disparities, including prostate, oral, cervical, and colon cancers,” he says. ■

CRF INVESTIGATOR NAMED ONE OF POPULAR SCIENCE’S BRILLIANT 10
Dr. Victor Velculescu’s way of identifying cancer-related genes is brilliant—so said Popular Science magazine. He was named by the magazine in their second annual Brilliant 10, a survey of researchers and academicians in fields from geophysics to quantum origami to identify scientists whose work is, according to POPSCI’s editors, “just plain brilliant.” Victor Velculescu, M.D., Ph.D., associate professor of oncology and a CRF-funded investigator, made the cut. “It is maverick approach ushered in a new way to finger cancer genes,” reports POPSCI. “Velculescu decided that rather than the conventional approach of identifying genes and then trying to figure out their role, he wanted to catch cancer genes in the act and then identify them.” To do this, Velculescu developed a method known as SAGE for Serial Analysis of Gene Expression.

“Of the approximately 100,000 genes in the human genome, only a fraction are thought to be active in each type of cell, but there are several thousand different types of cells in the human body and each has a unique pattern of gene expression,” explains Velculescu. “SAGE allows us to study thousands of genes simultaneously, measure their expression, and quickly identify the genetic differences between normal and tumor cells.” In simple terms, SAGE works like the bar codes on products that are scanned at grocery store checkouts. Just as these accumulated bar code entries provide a picture of a store’s high and low-volume sales items, SAGE gives a picture of the cell’s gene expression pattern. A product frequently purchased would be equivalent to high expression; ones rarely purchased would amount to low expression.

The Maryland Cigarette Restitution Funds at Johns Hopkins

Maryland’s CRF Held as National Model
Tough economic times saw many states, who had promised to use the proceeds from the lawsuit against cigarette manufacturers to address the problems caused by cigarette smoking, begin to use the funds to patch holes in their state budgets. Maryland’s governor and legislators were one of the first and few to hold up their end of the bargain funding cancer research and providing free cancer screening and education to the poor and uninsured through the Cigarette Restitution Fund. Maryland was held as a model program as other states were chastised at Congressional hearings on November 12, 2003. Senator John McCain called the National Governor’s Association and National Council of State Legislators to task for not living up to their promises. “At the time of the settlement, there was general agreement that the money would be used for tobacco education and treatment of smoking-related illnesses,” said McCain. ■

Making Maryland the National Cancer Model
CRF Making Headlines in 2003
Making Maryland the National Cancer Model

“At the time of the settlement, there was general agreement that the money would be used for tobacco education and treatment of smoking-related illnesses.” —Senator John McCain (R) Arizona
NEW THERAPEUTIC TARGETS FOR COLON CANCER
Investigators from the Johns Hopkins Kimmel Cancer Center and Howard Hughes Medical Institute completed what is believed to be the first systematic analysis of a disease-related gene family. Their analysis, reported in the May 9, 2003 issue of Science, uncovered gene mutations, linked to more than 30 percent of colon cancers, which could serve as therapeutic targets.

The research team studied 182 human colon cancers to identify mutations in the tyrosine kinase (TK) gene family. TK genes are thought to be good therapeutic targets for managing cancer because the proteins they encode play key roles in controlling cell growth, differentiation, motility, and nearby tissue invasion. Although a few TK genes have been shown to be mutated in specific cancers, until now, no study has revealed how many or how often members of the TK gene family are altered in a particular cancer type, according to CRF investigator VICTOR E. VELCULESCU, M.D., PH.D.

“Until now, there have been no other major genetic events identified for common thyroid cancers,” says Velculescu. “Moreover, we have found a mutation of the BRAF (pronounced b-raf) gene in 68 percent of papillary thyroid cancers. These tumors account for about 20-35 samples of papillary thyroid cancers. T he tumors account for about 20-35 percent of all thyroid cancer and occur mostly in women. “Until now, there have been no other major genetic events identified for common thyroid cancers,” says CRF investigator DAVID SIDRANSKY, M.D. “Our goal is to find better diagnostics and drug therapies designed to target the effects of this mutation.”

COMMON THYROID CANCER GENE MUTATION FOUND
Researchers found that a single genetic mistake causes about two-thirds of papillary thyroid cancers. Their research, published in the April 16, 2003 issue of the journal of the National Cancer Institute, may lead to new therapies that could counteract the mistake.

They found a mutation of the BRAF gene in 68 percent (24 of 35 samples) of papillary thyroid cancers. These tumors account for about 30 percent of all thyroid cancer and occur mostly in women. “Until now, there have been no other major genetic events identified for common thyroid cancers,” says Velculescu investigator DAVID SIDRANSKY, M.D. “Our goal is to find better diagnostics and drug therapies designed to target the effects of this mutation.”

POSSIBLE THERAPEUTIC APPLICATION
These findings are particularly relevant for urban communities where people live in close proximity to high volume roadways, says Buckley. “In Baltimore’s urban communities, as with many other U.S. cities, many people live near busy streets. What’s more, in many communities, the curbside stoop provides a venue for socialization, recreation or relief from summer heat, increasing their exposure potential to carcinogens,” he says. The models created from Buckley’s study will help evaluate exposure, risk, and control strategies in urban environments.

CLEANING UP THE ENVIRONMENT COULD HELP
“CLEAN UP” CANCER IN THE CITY
Assessing a community’s cancer risk could be as simple as counting the number of trucks and cars that pass through the neighborhood, according to Johns Hopkins Bloomberg School of Public Health researcher TIMOTHY BUCKLEY, PH.D. The CRF investigator identified a significant association between vehicle traffic and curbside concentrations of the carcinogens benzene, 1,3-buthadiene, and particle-bound polycyclic aromatic hydrocarbons (PAH). Buckley and his colleague measured levels of these carcinogens at a tollbooth at Baltimore’s Harbor Tunnel. Pollution levels varied six to 20 fold depending on traffic volume and vehicle type, with the highest levels measured during morning rush hour and the lowest in the middle of the night. Large vehicles, such as buses, motor homes, and tractor trailers were, not surprisingly, found to emit the greatest amounts of carcinogens.

Currently, the genetic marker blood tests are for research purposes only. More efficient tests will take several more years to develop and must be studied in patients over time to see if they accurately predict colon cancer development.

In Baltimore’s urban communities, the curbside stoop provides a venue for socialization, recreation or relief from summer heat, and increases their exposure potential to carcinogens.
Colon cancer is among the most common of all cancers. Johns Hopkins studies of this cancer revealed it, as well all other cancers, as a genetic disease by pinpointing a series of genetic alterations that lead to colon cancer.

Identification of the genetic mutations involved in the origination and progression of colon cancer could lead to a non-invasive test to detect the disease in an early, curable stage.

A stool test that detects precancerous polyps in the colon and very early colon cancers was developed based on Velculescu and team's mutational analysis of colon cancers. The test was licensed to and now distributed by Exact Science Corporation. The test is now available to the general public and has been added to the American Cancer Society's colon cancer screening guidelines.
MAKING THE CONNECTION: RESEARCH
TRANSLATION
APPLICATION
CRF INVESTIGATOR
VICTOR VELCULESCU
IN THE COMMUNITY
Rodney Scruggs
Prostate Cancer Survivor
As an African American man, Rodney Scruggs knows the importance of being screened for prostate cancer. He has even been screened before. When it was again time for his regular screening, however, he did not call his doctor because he had been laid off from his job and had no insurance. Fortunately, he heard about the Johns Hopkins/CRF prostate cancer screening program on a talk radio station and made an appointment. It turned out that Rodney had prostate cancer. Because his cancer was detected early through screening, this story has a happy ending. The Johns Hopkins surgeon that operated on him in October 2004 believes he got all of the cancer.
By the Numbers

7 Targeted Cancers:
- Breast cancer
- Cervical cancer
- Colorectal cancer
- Lung cancer
- Melanoma skin cancer
- Oral cancer
- Prostate cancer

Research:
- $2.59 million research dollars awarded
- 5 faculty recruited
- 5 faculty retained
- 4 translational research awards

Prostate Cancer Prevention, Education, Screening and Treatment:
- $1.4 million public health grant awarded
- 506,050 people reached through media
- 16,048 people educated
- 585 cancer screenings
- 3 men diagnosed and treated for prostate cancer
2004 RESEARCH AWARDS

MARYLAND QUICKLY stood out as a national model when it was among the first states to put its tobacco money into the Cigarette Restitution Fund, directly targeting cancer problems specific to Maryland, including high rates of smoking-related cancers, providing cancer education, screening, and treatment to the state’s uninsured, taking on Baltimore’s high rate of prostate cancer—the highest in the nation, and Maryland’s excess cancer risk and deaths due to air pollution.

MUCH NEEDED TREATMENT STRATEGIES FOR LUNG CANCER

The main goal of the Multidisciplinary Translational Program for the Development of Treatment Strategies for Lung Cancer is to build stronger connections between laboratory and patient-based research, according to program director Charles Rudin, M.D., Ph.D. Working collaboratively with researchers and clinicians throughout the institution involved in lung cancer work, his team applied basic science knowledge about the genetic and cellular steps that lead to the initiation and progression of lung cancer to improve early detection and risk assessment. Clinical trials already planned include a study of the drugs Bevacizumab and Celecoxib for their ability to interfare with cellular changes linked to lung cancer and a study of the drug Erlotinib in patients with advanced non small cell lung cancer (NSCLC).

CANCER PREVENTION IN AFRICAN-AMERICAN YOUNG ADULTS

The cancer burden is particularly problematic for the African-American population, as African-American men are 50 percent more likely to develop lung cancer than white men. In addition, African Americans have higher death rates from lung and bronchial cancers when compared to white Americans. In addition, African Americans have likely to develop lung cancer than white Americans. The study data was used among 18- to 24-year-old blue-collar African Americans. The study data was used to develop appropriate and culturally relevant intervention strategies for this group. This research also received CRF funding in 2007.

TURNING RESEARCH INTO RESULTS

Research directed by Kathy Helzlsouer, M.D., M.H.S., applied an evidence-based approach, incorporating cost-effectiveness measures, to develop a priority list of cancer control interventions and strategies for public dissemination. The evidence-based rankings were compared with rankings of the committees contributing to the Maryland Cancer Control Plan. Two priority rankings were developed, one for the areas where evidence of effectiveness already exists and another for areas where research is needed. Priorities will be ranked by levels of evidence as well as public health impact and should aid in the translation of research to community interventions.

UNDERSTANDING THE CANCER BURDEN IN MARYLAND

Research by Ann C. Klassen, Ph.D., was aimed at improving patterns of cancer-related outcomes among the States disadvantaged populations, including African Americans, elderly, new immigrant groups, and residents of low-resource communities. This work contributed to theory and methods for social sciences and cancer control and answered specific questions of regional and community significance, such as the assessment of local cancer control needs and the evaluation of local service programs.

ARSENIC EXPOSURE AND CANCER RISK IN MARYLAND

Ellen K. Silbergeld, Ph.D., tested the hypothesis that environmental arsenic exposures from poultry production contributes to the increased rates of smoking-related and other cancers among people living on the Eastern and Western Shores of Maryland. Arsenic is a known human carcinogen, and increased risks of skin, bladder and lung cancers have been associated with contaminated drinking water exposure. Low levels of arsenic exposure increase the carcinogenic effects of UV rays and chemicals in cigarette smoke by inhibiting DNA repair. Silbergeld and team defined and mapped environmental sources of arsenic exposure, examined pathways of exposure—particularly contamination of drinking water—and studied the use of biomarkers to evaluate arsenic exposure and susceptibility.

THE MARYLAND CIGARETTE RESTITUTION FUNDS AT JOHNS HOPKINS
ESHELMAN, M.D., PH.D., and team of these drugs could increase the effectiveness of treating tumors. Investigators hope to identify how drugs that decrease NHEJ efficiency and increase the effectiveness of treating tumors. Investigators hope to identify how drugs that decrease NHEJ efficiency and may provide new clues about the development of tumors. Deciphering how it works, and understanding NHEJ at the molecular level. NHEJ is a key step in the repair of double-strand breaks in DNA, which is central to maintaining the integrity of genes. This repair mechanism may be affected by a biochemical process known as NHEJ (Non-Homologous End Joining). Research by LES HASAN, M.D., Ph.D., revealed a new understanding of NHEJ at the molecular level. Understanding how it works, and more importantly, how it sometimes fails, may provide new clues about the development of tumors. Investigators hope to identify drugs that decrease NHEJ efficiency and affect gene integrity in cancer cells. The use of these drugs could increase the effectiveness of radiation therapy by making cancer cells unable to repair damage after treatment.

IDENTIFYING ABNORMAL GENES IN PANCREATIC CANCER

The identification of a familial pancreatic cancer gene would be a major advance in understanding pancreatic cancer. A novel approach called GINI (Gene Identification through Non-allelic Differential Delay Inhibition) was used to identify gene abnormalities linked to prostate cancer and JIM EHLER, M.D., Ph.D., and team believe it also could help identify genes whose altered expression patterns are potential culprits in pancreatic cancer.

HORMONES AND PROSTATE CANCER

This study brought together investigators from a wide range of disciplines to conduct research on hormones related to prostate cancer. The project, led by ELIZABETH PLATZ, S.C.D., M.P.H., provided new information on the role of sex steroid hormones in the origination of prostate cancer and other important diseases of aging men. Hormonal differences, at different ages, are suspected to account for race and ethnic differences in the occurrence of prostate cancer.

IMPROVING ACCESS TO CARE

Steven Piantadosi, Ph.D., and team focused on cultural and other factors that may cause treatment delays or block access to care. A collaborative study that used various data sources provided a detailed view of the Kimmel Cancer Center patient population and revealed why and how patients make choices about where they go for cancer care.

THE CORE OF CANCER RESEARCH

To address environmental health issues, more and more investigators are turning to molecular technologies. Shyam Biswal's DNA microarray core facility allows investigators to uncover the function of genes and their interaction in genetic pathways, among other analyses. This new facility has already been useful in helping uncover novel targets for drug interventions, including Nrf2, which has had a major impact on stress pathways research in cancer. These technologies also have been used to explore gene expression alterations resulting from human fetal exposure to drinking-water carcinogens. Biswal has used core technology to pinpoint genetic susceptibility factors for chronic obstructive pulmonary disease, a risk factor for lung cancer.

URBAN FISHING

Ellen Silbergeld, Ph.D., brought attention to urban fishing, an under-recognized environmental risk. Urban waterways are often jeopardized by sewer overflows, garbage dumping, domestic animal waste, storm water runoff, lawn chemicals, disposition of air pollutants, and leaks from an aging sanitary infrastructure. Silbergeld finds that the contamination goes beyond chemical to microbiological and that consumption of fish from these waterways is not the only risk. Normal hand-to-mouth activities in fishing, such as eating, smoking, bathing, and taking fish off of hooks, transfer pathogens, including viruses, microparticles, and pathogenic bacteria as well.

AT THE CORE OF CANCER

The scientific foundation of cancer prevention is continually being shaped by new technologies. Among these new technologies is the study of cancer-related proteins found in human plasma, and a new plasma proteomics core facility was constructed to provide a powerful way to explore the influence of environmental agents on the human body. The facility has electrophoresis, scanning, and data equipment interfacing with existing technologies and imaging for protein discovery and understanding. The result, say researchers JOHN GROOPMAN, PH.D., and James D. Yager, Ph.D., will be new insights into the contribution of environmental chemicals—particles, metals, and dietary carcinogens—to the formation of cancer so that we can develop more rational approaches in prevention.

5 APPLES A DAY COULD KEEP CANCER AWAY

Epidemiological evidence suggests that fruits and vegetables reduce the risk of getting cancer and other chronic diseases. Unfortunately, current data also show that only about 39 percent of Americans think they should eat at least five servings daily, and the numbers are even lower among African-Americans and low-income populations. CRF investigator Ann Klassen, Ph.D., has begun an educational program to encourage better eating habits among African-American women living in public housing in urban areas.

SMOKING CAUSES CANCER, BUT NOT IN EVERYONE

While more than 80 percent of chronic obstructive pulmonary disease (COPD) and lung cancer patients are smokers, only 15-20 percent of smokers get COPD and only 10-15 percent of smokers get lung cancer. Shyam Biswal, Ph.D., sought to find out why to uncover the body's own defense mechanisms against environmental triggers and identify those genetically predisposed to smoking-related diseases, such as lung cancer. Because the genetic factors that contribute to susceptibility are largely unknown, he continues to sift through candidate genes. His breakthrough study in 2002 showed that activation of a master gene, Nrf2, can turn on antioxidant genes. Using this paradigm for investigating cigarette smoke effects on lungs and genes, Biswal's research focused on enumerating the genes controlled by Nrf2 and their role in causing disease. Nrf2, he conducted a whole-genome assessment for mutagenic influences of Nrf2, in search of ways to fight drug resistance and oxidative cell damage, to mitigate damage caused by cigarette smoke and other environmental factors.
CANCER'S RESISTANCE
BREAKING BREAST
CANCER'S RESISTANCE
Hormonal therapy has been quite effective in treating women with hormone-responsive breast cancers. The drug tamoxifen, the standard choice for hormonal therapy, has helped decrease recurrence rates and the spread of breast cancers. Unfortunately, in many women, after a period of time, cancer cells become resistant to the drug, and it no longer works. With combined funding from the CRF, Avon Foundation, and Flight Attendant Medical Research Institute, breast cancer researcher BEN PARK, M.D., is purchasing chemical drug libraries to screen for compounds that specifically kill or inhibit the growth of tamoxifen-resistant cancer cell lines without interfering with cells responsive to tamoxifen. Adding such a drug to therapy could potentially be a major breakthrough in treating hormonally-resistant breast cancers.

DHMI STUDY REPORTS
DROPS IN SMOOKING RATES
Smoking rates for Maryland's adults and teens declined significantly over a two-year period, according to a study by the Department of Health and Mental Hygiene. Among those under 18, smoking dropped by 14 percent. For adults, smoking declined by 9 percent. Study results were reported in the Baltimore Sun on January 15, 2004.
For their report, department of health researchers interviewed more than 66,000 middle and high school students and 15,000 adults statewide between 2000 and 2002.
"Maryland is one of the most progressive states in tobacco prevention," said FRANCIS STILLMAN, a CRF investigator focusing on smoking cessation. "The smoking decreases the study identified were significant, particularly among young people." According to the study, just under 20 percent of Maryland adults smoke, about 3 percent lower than the national average. For those under 18, smoking rates dropped from 21.4 percent in 2000 to 18.4 percent in 2002.
Maryland's tobacco control programs are supported by the Cigarette Restitution Fund.

MARYLAND'S ELECTED OFFICIALS
HONOR TOBACCO SETTLEMENT COMMITMENT
An article in the January 15, 2004, issue of the New England Journal of Medicine reported on many states use of tobacco settlement funds to fill budget gaps. "It's moral treason," said Mississippi attorney general M. ichael Moore. "It's unfortunate that more states were not committed to cancer control. The losers are the people in states where legislators have chosen to spend the money on budget deficits instead of long-term investment in health." Maryland used the settlement as it was intended, and is seen as a national model, establishing the Cigarette Restitution Fund to for cancer research, education and screening.

REPORT ON BREAST CANCER
The Institute of Medicine of the National Academies released a new report: Saving Women's Lives: Strategies for Improving Breast Cancer Detection and Diagnosis. The report, authored by a diverse committee comprising the world's leading experts on breast cancer detection, including Kimmel Cancer Center director and CRF co-director MARTIN ABELOFF, M.D., is the most in-depth examination to date of what can be done to improve breast cancer screening and detection services in the United States. The committee's recommendations provide a blueprint for expanding and enhancing the quality of breast cancer screening.

TAKING THE CRF MESSAGE TO THE HILL
LES HANAKAHI, M.D., is the most in-depth examination to date of what can be done to improve breast cancer screening and detection services in the United States. The committee's recommendations provide a blueprint for expanding and enhancing the quality of breast cancer screening.

ELLEN SILBERGELD IS NOT "TOO CHICKEN" TO TELL IT LIKE IT IS
ELLEN SILBERGELD says the poultry industry's widespread use of drugs to raise chickens is exposing people who eat them to more arsenic than previously reported. The May 4, 2004, Baltimore Sun reported on the findings of CRF investigator Ellen Silbergeld, a toxicologist who won the MacArthur Foundation "genius award" for prior work linking mercury pollution with infectious diseases.
Arsenic-laced drugs, designed to keep chickens healthy, might increase cancer risks for consumers and create manure that is contaminating Maryland's Eastern Shore ground water, according to Silbergeld's research. Despite disagreement from the government and poultry groups, she's not about to let up. She charges that the USDA underestimated the amount of arsenic found in chickens and used outdated data to estimate the health risks of ingesting arsenic in a report issued last January. While a spokesman for the poultry industry calls Silbergeld's concerns about arsenic unfounded, Silbergeld says they could have major implications for the Eastern Shore, where 10 percent of the nation's poultry is raised.
Advances in Cancer Research, Treatment, and Prevention

MOLECULAR “MAGNET” MAY BE NEW DIAGNOSTIC TOOL FOR CANCER
A new molecular tool dubbed “LigAmp” appears to be able to pinpoint DNA mutations among thousands of cells, making it possible to detect microscopic cancer and even HIV drug resistance. The tool can even create a molecular “magnet” that attaches itself to DNA mistakes known as point mutations. Once attached, it inserts a bacterial gene that produces a fluorescent color visible to physicians through special computerized equipment. “The molecular code of normal cells may look identical to cancer cells except for a single rung in the DNA ladder structure. The test finds that one defective rung,” says CRF investigator JAMES ESHELEMAN, M.D., PH.D., an expert on DNA diagnostics. Esheleman says such a test would be useful in monitoring for cancer in high-risk patients, detecting cancer recurrences early and treating HIV patients.

DRUG STABILIZES SPREAD OF PROSTATE CANCER
CRF investigator MICHAEL CARDUCCI, M.D., reported that the drug atrasentan stabilizes the spread of cancer in many men with advanced prostate cancer who have stopped responding to hormone therapy. The three-year international study of more than 1,000 men opens the door to potential new treatment options for this subset of patients. “Some of these men are looking for less-toxic alternatives to chemotherapy at this point in their lives,” says Carducci. “By keeping the cancer from spreading to the bone, atrasentan can help prevent their pain and potentially postpone when they will need more aggressive treatment,” he says.

HIGH BLOOD TESTOSTERONE = INCREASED PROSTATE CANCER RISK
Men over 50 years of age with high blood levels of testosterone have an increased risk of prostate cancer, according to a study by researchers at Johns Hopkins and the National Institute on Aging. The finding throws some doubt on the safety of testosterone replacement therapy, the investigators say.

The researchers, including CRF investigator ELIZABETH PLATZ, PH.D., measured several forms of testosterone in almost 3,000 blood samples collected over a 40-year period from 759 men in the Baltimore Longitudinal Study on Aging, of whom 111 were diagnosed with prostate cancer. One form of testosterone, called free-testosterone, which is biologically active and can actually be used by the prostate, was found to be associated with increased prostate cancer risk.

BLOOD TEST FOR LIVER CANCER RISK
Johns Hopkins Kimmel Cancer Center scientists led by JOHN GROOPMAN, PH.D., Johns Hopkins CRF co-director developed a blood test that can predict some future cases of liver cancer in hepatitis B patients. The test is based on a biomarker that detects mutations in the hepatitis B virus (HBV) that tend to speed up cancer development in people who test positive for the virus. “We can use this biomarker to identify patients who may be good candidates for liver cancer prevention studies,” says Groopman.

SWITCHED-OFF GENES PUT BRAKES ON CANCER
CRF researcher STEPHEN BAYLIN, M.D., and team identified a switched-off family of genes that may put a significant and early dent in a colon cell’s anti-cancer armor. The inactivated genes, called SFRPs—for secreted frizzled-related protein—put the brake on a pathway of cell-growth genes that is an early step in the cancer process.

Because of the way SFRP genes are activated—or through the attachment of so-called methyl groups—it is reversible, the findings, reported in the March 14, 2004, advance online edition of Nature Genetics, also suggest potential anti-cancer value in green tea and other compounds that affect methylation.

NEW CANCER GENE TARGET
A CRF investigator identified mutations in a gene known as PIK3CA and linked them to the progression of colon and other cancers. The researchers say their discovery identifies this gene as one of the most highly mutated genes in human cancer that could serve as a target for new cancer treatments. The PIK3CA gene is part of a family of genes that encode lipid kinases, enzymes that modify fatty molecules and direct cells to grow, change shape or move. “Kinases have been the focus of recent drug development strategies, with some kinase-inhibiting compounds, like Gleevec and Herceptin, already being used in patients to block tumor growth,” says VICTOR VELCULESCU, M.D., who led the study. Velculescu and team are now studying the role of the gene in tumor progression more closely and working to identify drugs to target tumors with the mutation.

INFLAMMATION MARKER PREDICTS COLON CANCER
C-reactive protein (CRP)—a marker of inflammation circulating in the blood already associated with increased risk of heart disease—can also be used to identify a person’s risk of developing colon cancer, according to a Johns Hopkins study directed by CRF investigator THOMAS “TA TE” P. ERLINGER, M.D., M.P.H.

Results of the study, published in the Feb. 4, 2004, issue of The Journal of the American Medical Association, showed that over an 11-year period, people with higher levels of CRP in their blood (a median of 2.44 milligrams per liter) were more likely to develop colorectal cancers than those with low levels of CRP (a median of 1.94 mg/L).

It’s not clear yet how or whether changes in CRP levels could serve as a target for new cancer therapies and team are now studying the role of the gene in tumor progression more closely and working to identify drugs to target tumors with the mutation.
Survival from lung cancer, caused by cigarette smoking, has been difficult to achieve because resistance to current cancer drugs develops. Each year in the U.S., nearly half a million people die of smoking-related diseases. Keap1 mutations and the NRF2 pathway are implicated in lung cancer and chronic obstructive pulmonary disease.

TRANSLATION
A cigarette exposure facility is constructed to study smoke-induced lung cancer and uncover protein biomarkers for the cancer. The protein Nrf2 is identified and found to pump out carcinogens, including therapeutic anticancer drugs.

APPLICATION
Biswal, working with Geoffrey Gumin from University of Maryland, begin screening 1280 compounds that can knock down NRF2 in patients. The best candidate will be used in lung cancer patients to block resistance to chemotherapy.

TIMELINE OF DISCOVERY

Lung Cancer

CRF INVESTIGATOR: SHYAM BISWAL, PH.D.

2001
Cigarette exposure facility is constructed to study smoke-induced lung cancer and uncover protein biomarkers for the cancer. Cancer-causing constituents are quantified, including carbon dioxide, nicotine and acrolein in smoke.

2002
Biswal’s work revealed new information about smoking related carcinogens and the cellular changes that ultimately result in cancer. His findings are reported in two scientific journals and at the Society of Toxicology annual meeting. This work led to a lung cancer project in the National Cancer Institute Specialized Program Of Research Excellence.

2003
The facility allows researchers to identify and test chemopreventive agents that block the negative impact of smoke on cells. They also have begun to pinpoint specific cellular changes that could serve as biomarkers for the early detection of lung cancer. A National Institute Health investigator initiated research grant was funded.

2004
The protein Nrf2, studied in the exposure facility and found in animal models to alter the lungs response to cigarette smoke, is target for cancer prevention drug trials.

2005-2007
Another gene, Keap1 gene is identified as NRF2’s co-conspirator. Keap1, lets cells know when the toxins are removed, shutting down NRF2 and stopping the cell cleansing process. He finds NRF2 directs proteins to absorb pollutants and chemicals and then pumps them out, clearing cells of toxins.

Lung cancer cells corrupt the process. An altered Keap1 gene keeps the NRF2 gene active and pumping out cancer-attacking drugs before they can get into cancer cells. This work earned additional grants from NIH and the Flight Attendant Medical Research Institute.

JHU has been granted two international patent applications. The first invention is going through the second year of sponsored project with a pharmaceutical company which has an option to license from JHU. The second invention has led to a university faculty start up company AImmune, Inc., located in the JHMI Science & Technology Park. This company is in negotiation with JHU for licensing the invention for commercialization.

2008
Biswal tests a compound that blocks NRF2 in lung cancers with Keap1 mutations, in combination with anticancer drug carboplatin to target the cancer while blocking treatment resistance. A clinical trial has been funded by NCI to improve chemotherapy in lung cancer targeting the Keap1 mutation.
MAKING THE CONNECTION: RESEARCH TRANSLATION APPLICATION

CRF INVESTIGATOR
SHYAM BISWAL
IN THE COMMUNITY

Maurice Johnson
Screened for Prostate Cancer

“I got tested at Liberty Heights. I’m a walking testimony to the importance of prostate cancer screening. It saved my life!”
2005

By the Numbers

7 Targeted Cancers:
- Breast cancer
- Cervical cancer
- Colorectal cancer
- Lung cancer
- Melanoma skin cancer
- Oral cancer
- Prostate cancer

Research:
- $2.41 million research dollars awarded
- 6 faculty members recruited
- 1 faculty retained
- 4 translational research awards

Prostate Cancer Prevention, Education, Screening and Treatment:
- $1.2 million public health grant awarded
- 1,051,000 people reached through media
- 15,366 people educated
- 675 people screened
- 5 men diagnosed and treated for prostate cancer
 telomere shortening. With mutations in telomerase, however, chromosome ends fray at the borders of needed genes. With mutations in telomerase, known as idiopathic pulmonary fibrosis in two genes that regulate the enzyme telomerase, which keeps chromosome ends fray and wear down each time a cell divides. The mutations were spotted in two genes that contain repetitive bits of DNA code that help lengthen the fragile ends of chromosomes. Chromosome ends, or telomeres, contain repetitive bits of DNA code that help lengthen the fragile ends of chromosomes. Chromosome ends, or telomeres, contain repetitive bits of DNA code that help lengthen the fragile ends of chromosomes. Chromosome ends, or telomeres, contain repetitive bits of DNA code that help lengthen the fragile ends of chromosomes. Chromosome ends, or telomeres, contain repetitive bits of DNA code that help lengthen the fragile ends of chromosomes.

A novel area of gene research is relating the expression from thousands of gene sequences to how advanced or aggressive a cancer is and predicting how it may react to exposure to anticancer drugs. Though genetic research has uncovered countless genes related to the cancer process, many investigators have been left with data on thousands of genes with no statistical method for analyzing the data. The investigators, directed by GIOVANNI PARMIGIANI, PH.D., have developed a statistical method for analyzing data from as few as a single gene sample. The method has already been used successfully to identify genes associated with T cell pathways and in stem cell research. The method has also been applied to gene studies of skin cancer, papillary thyroid cancer, and Alzheimer's disease. The scientists built upon this success by further refining their analysis of gene expression to better understand and characterize the differences, or subtypes, within specific cancers and other diseases.

HELP IN THE FIGHT AGAINST LUNG CANCER

Hopkins Early Lung Cancer Prevention Program (HELP) is a comprehensive program that encompasses translational and community-based research. HELP studies include basic laboratory genetic research, new investigational drugs, and an outreach prevention program with study participants representative of minority groups throughout Maryland. “Each of our investigators brings an appropriate mix of laboratory and clinical experience to the team,” says JULIE N. BRAHMER, M.D., a co-director of HELP.

“Our goal is to make a much needed impact on lung cancer incidence and death rates by being a driving force in prevention studies, both at our own institution and as collaborators in national studies,” says Brahmer.

Several potential prevention strategies were tested. The drugs Iressa and Zarnestra were studied in current and former smokers for their ability to halt early cellular changes caused by smoking that can lead to lung cancer. A national collaborative study focused on the drug Iloprost, which may be able to reverse cellular changes in the bronchial lining that often appear as a precursor to lung cancer. Investigators continue to study sulforaphane, a broccoli extract, that detoxifies the carcinogens that lead to lung cancer initiation.

GETTING TO THE CORE OF CANCER

With the ever-growing list of genetic targets being investigated, there became a growing need for readily accessible and well-characterized biological samples from cases and controls to move these findings from the research phase to cancer detection and treatment for people. The Cancer Prevention and Control Resource Core, directed by ELIZABETH PLATZ, S.C.D., M.P.H., addressed this need by centralizing the collection of blood samples and health and self-reported exposure data from consenting cancer patients seen at the Kimmel Cancer Center, as well as from consenting relatives and friends of patients as a ready source of controls. This Core enhances cancer biomarkers research by permitting investigators to quickly identify appropriate blood samples of well-characterized individuals, allowing studies of biomarkers to be conducted rapidly, efficiently, and cost effectively.
KNOCKING DOWN BARRIERS TO CARE

Medically underserved populations are those that lack easy access to, or do not make use of, high-quality cancer prevention, screening and early detection, treatment, or rehabilitation services. According to the National Cancer Institute (NCI), in general, these groups experience higher cancer death rates than the U.S. population as a whole. In addition, many of these populations remain under-represented in NCI-funded cancer clinical trials. Steps towards participation in clinical trials include awareness, acceptance, and retention. Unfortunately, there is limited information about evidence-based strategies for recruitment of underserved populations into cancer-related trials.

JEAN FORD, M.D. and MOLLIE HOWERTON, PH.D., worked to identify and understand the barriers to care and increase participation in cancer prevention and treatment trials.

TRANSLATIONAL LUNG CANCER RESEARCH

CHARLES RUDIN, M.D., developed a translational lung cancer program in 2003 and continued the program with CRF funding. Rudin has begun studies of the pathways involved in cell death and how these pathways can be exploited to improve lung cancer therapy. New research focuses on a small molecule that targets a gene known as BCL2. Inhibiting BCL2 could increase therapeutic sensitivity in small cell lung cancer.

THWARTING A CANCER-CAUSING VIRUS

Oral HPV (human papillomavirus) infection is a recently recognized public health problem. This is in great part due to the work of Johns Hopkins CRF investigator MAURA GILLISON, M.D., PH.D. She was the first to definitely link infection with HPV to oral cancers and to uncover how it works in correlation with other known risk factors, like tobacco and alcohol, to impact treatment prognosis.

Gillison is particularly interested in cancer of the tonsils, which is on the rise in American men with HIV (human immunodeficiency virus). She suspects that immune suppression caused by HIV makes individuals more susceptible to oral HPV infection.

Working in conjunction with Johns Hopkins HIV clinic, she has begun the Human Oral Papillomavirus Etiology (HOPE) project and hopes to follow 800 HIV-infected men and women. More than 200 patients have already enrolled. Patients will be followed for four years so investigators can observe the natural history of HPV infection and how sexual behavior, smoking, and alcohol use impact its progression to oral cancer. Gillison believes the study will generate information key to the care of individuals with joint HPV and HIV infection, a population expected to grow considerably in the coming years.

CANCER TESTS

DAVID SIDRANSKY, M.D. is the nation’s leading expert in isolating DNA from blood, tissue, and body fluids to examine them for genetic and epigenetic alterations indicative of cancer. This success has led to high demand on his laboratory. CRF funding is helping expand his laboratory so that he can provide investigators throughout Johns Hopkins with timely molecular tests targeted to newly discovered biomarkers to determine their feasibility as screening tests for cancer.

Our goal is to make a much needed impact on lung cancer incidence and death rates by being a driving force in prevention studies, both at our own institution and as collaborators in national studies.
Cutting Cancer Risks, Solving Cancer Mysteries

DETOXIFYING PROSTATE CANCER CELLS
Investigators studied an enzyme called GSTP1 that may protect prostate cancer cells against environmental damage from smoke and other chemicals. The enzyme was found to play a key role in preventing precancerous prostate lesions from turning malignant. When functioning correctly, the gene appears to detoxify carcinogens. However, in people with prostate cancer, the gene may have been deactivated. Investigators are exploring the possibility of therapeutically inducing protective enzymes that would restore and/or compensate for missing or low levels of the enzyme GSTP1.

HELPING KICK THE HABIT
Free nicotine patches, funded by the Maryland CRF, were distributed to smokers in a joint study by Johns Hopkins and the Washington County Health Department. The patches increased the number of participants in cessation programs and helped 27 percent more people quit smoking, at least for a period of time, says Johns Hopkins CRF investigator ANTHONY ALBERG, PH.D., M.P.H.

SIZE MATTERS: SHORTENED CHROMOSOMES ARE A SIGN OF EARLY CANCER
Just as the plastic protective coverings on the end of shoelaces protect the laces, telomeres, the end caps on chromosomes, preserve genetic integrity. CRF researcher ANGELO DEMARZO, M.D., PH.D., and Alan Meeker, M.D., Ph.D., have evidence that they play a role in the early development of many types of cancer. The investigators studied tissue taken from small precancerous lesions in the bladder, esophagus, large intestine, mouth and cervix and found shortened telomeres 97 percent of the time. Telomeres protect the interior, gene-containing parts of the chromosome from being accidentally lost. As normal cells divide and age, some of the telomere DNA is lost, and the telomeres get progressively shorter. Normal cells monitor the length of their telomeres and initiate cell death if they get too short. If this monitoring system breaks down, cancer can be initiated. Assessing telomere length may provide a new direction for cancer prevention and early diagnosis studies, says DeMarzo.

SOLVING THE MYSTERY OF THE DISAPPEARING CERVICAL PRECANCERS
CRF research shed light on why cervical precancers disappear in some women and not in others and helped pinpoint which women would benefit from a cervical cancer vaccine developed and studied at the Kimmel Cancer Center. The strain of HPV and the genetic characteristics of a woman’s immune system seem to be the key. The lifetime risk of becoming infected with a high-risk strain of HPV, at least once, is over 80 percent, so why do only a small percentage of these infections progress to full-blown cancer? In her study of 100 women with high-grade precancerous lesions, CONNIE TRIMBLE, M.D., is studying immunologic characteristics that may help solve this mystery and identify women whose immune system may need help to get rid of the cervi-
INCREASED CANCER RISK
MARYLAND’S POOR HAVE
INCREASED CANCER RISK
FROM AIR POLLUTION
Maryland communities that are poor and
predominantly African-American incur a
disproportionate cancer risk from
ambient exposure to airborne toxins,
according to Johns Hopkins researchers,
including CRF Investigator TIMOTHY
BUCKLEY, PH.D., M.H.S. Their
study revealed that among Maryland cen-
sus tracts, the poorer the community and
the higher the proportion of African-
Americans, the greater the residents’
risk for advanced disease in half," says
ELIZABETH PLATZ, SC.D., M.P.H.
Although earlier, smaller studies have
linked the use of statins to a lower risk of
prostate and other cancers, such as breast
and colon, this was the first to tie risk
reduction to prostate cancer stage while
tracking the medication use before study
participants got cancer.
Still, the researchers caution that data
are not conclusive enough to warrant
prescribing the drug to reduce cancer risk
alone because many questions still linger,
such as how they might contribute to
delaying the cancer process more effec-
tively than non-statins.

New CRF research sheds light on why
cervical precancers disappear in some women
and not in others and helps pinpoint which
women would benefit from a cervical cancer
vaccine under development and study at the
Kimmel Cancer Center.

STATINS HELP CUT RISK OF
ADVANCED PROSTATE CANCER
In a 10-year study of more than 30,000
health professionals, researchers at Johns
Hopkins and Harvard found that the
longer men take cholesterol-lowering
drugs such as statins, the far less likely
they are to develop advanced prostate
cancer.
“We found that statin-takers cut their
risk for advanced disease in half,” says
CHARLES DRAKE, M.D., PH.D., director of this research
published in Cancer Cell.
The researchers’ results also corroborate
past studies that found an association
between active cigarette smoking and cervical neoplasia — the growth of a
tumor. The concept of the Johns Hopkins
study was the result of collaboration among
several researchers supported by the
Maryland Cigarette Restitution Fund.

EARLIER USE OF PROSTATE
CANCER VACCINES URGED
Timing is everything when it comes to
killing prostate cancer cells with specially
tailored vaccines, say scientists testing the
drugs in mice. “The window of opportu-
nity is narrow for vaccination, designed to
reinvigorate the immune system’s
attack on cancer cells, and it occurs right
after hormonal therapy begins to wipe
out the tumor and immune cells out-
number cancerous ones,” according to
CRF Investigator JULIE LAMBERTSON,
PH.D., M.S., an assistant professor of
Surgery at Johns Hopkins.

CRF INVESTIGATORS RECEIVING HONORS AND AWARDS
STEPHEN B. BAYLIN, M.D., was awarded the 2005 Simon M. Shubitz Cancer Prize
and Lectureship awarded in honor of the late Simon Shubitz, a distinguished alumnus of the
University of Chicago, and given in recognition of excellence in cancer research.
KALA VISVANATHAN, M.B.B.S., F.R.A.C.P., M.H.S., was one of 13 recipi-
ents of the American Society of Clinical Oncology Young Investigator Cancer Development
Awards. Visvanathan received $170,000 as part of a three-year grant.
LEISHA EMENS, M.D., PH.D., received the AVON Clinical Trials Award for her
work on a breast cancer vaccine.
The Maryland Cigarette Restitution Funds at Johns Hopkins

A drug that helps block prostate cancer

In as many as 85 percent of men with hormone-therapy-resistant prostate cancers, the cancer spreads to their bones. The pain associated with this spread has been likened to being stung repeatedly by wasps.

**Translation**
Researchers link the protein endothelin to prostate cancer progression and the painful metastasis to the bone. In a study of 2,000 men, they find the drug atrasentan, one of the first “targeted” cancer therapeutics, blocks endothelin.

**Application**
The drug goes before the FDA for first review. Though the FDA denies approval pending additional safety and efficacy studies, clinical trials begin for men with hormone-therapy-resistant prostate cancer that has not yet spread to the bone in an effort to abate the painful progression of the disease.

**Timeline of Discovery**

**Prostate Cancer**

**CRF Investigator: Michael Carducci, Ph.D.**

1995
Kimmel Cancer Center researchers link the protein endothelin to prostate cancer progression and the painful metastasis to the bone.

1996-2004
Clinical trials of the prostate cancer drug atrasentan, which blocks endothelin, are held. More than 2,000 men participate.

2002
Michael Carducci, M.D., receives CRF support to continue studies of atrasentan.

2003
Investigators report that this drug, among the first of the “targeted” cancer therapeutics, blocks a protein called endothelin, secreted in excess amounts by prostate cancer cells, promoting prostate cancer cell growth and painful metastasis to the bone.

2004
Carducci reports the results of these trials to the American Society of Clinical Oncology. Findings show that the drug stabilizes the spread of cancer in 20 percent of men with advanced prostate cancer whose disease has stopped responding to hormone therapy.

2005
In as many as 85 percent of men with hormone-therapy-resistant prostate cancer, the cancer spreads to their bones. Oncologists agree that the drug is a reasonable option for these men through clinical trials.

2006-2008
Clinical trials for men with hormone-therapy-resistant prostate cancer that has not yet spread to the bone.
MAKING THE CONNECTION: RESEARCH/TRANSLATION/APPLICATION

CRF INVESTIGATOR
MICHAEL CARDUCCI, M.D.
IN THE COMMUNITY

Yvette Griffin
Breast Cancer Screening

Yvette Griffin received a mammogram in February 2005 through an Avon Foundation-sponsored program leveraged through the CRF. She is now planning her current exam and feels proud that she is setting an example for daughter Tierra who has learned through Mom the importance of cancer screening.
2006
By the Numbers

7 Targeted Cancers:
  Breast cancer
  Cervical cancer
  Colorectal cancer
  Lung cancer
  Melanoma skin cancer
  Oral cancer
  Prostate cancer

Research:
  $1.8 million research dollars awarded
  6 faculty members recruited
  4 faculty retained
  4 translational research awards

Prostate Cancer Prevention, Education, Screening and Treatment:
  $1.2 million public health grant awarded
  540,000 people reached through media
  6,642 people educated
  588 people screened
  9 men diagnosed and treated for prostate cancer
AT THE CORE OF CANCER
Despite our great progress and a significant decline in cancer incidence and deaths in Maryland, cancer rates remain above the U.S. average. The cause of Maryland’s higher rates are largely unknown, so the identification of genetic and other biomarkers of risk is believed essential to developing clinical interventions for the prevention and early detection of cancer.

The Cancer Prevention and Control Population Resource Core, opened in 2004 and directed by ELIZABETH PLATZ, SC.D., M.P.H., and AVARINDA CHAKRAVARTI, PH.D., offers Johns Hopkins cancer researchers a centralized bank of blood samples and self-reported exposure data to quickly and efficiently identify biological markers of cancer risk and initiation. With continued CRF support, Core investigators and staff are now working to collect samples and information from 1,000 adults each year. Core samples are racially diverse, coming from Caucasians, African Americans, and Hispanics, and because the majority of participants are Marylanders, results of biomarker studies will directly apply to and benefit Maryland citizens.

This research also received CRF funding in 2003, 2005, and 2007.

CONQUERING A LETHAL CANCER
No cancer illustrates the need for early detection better than pancreatic cancer. Because it is almost always fatal, diagnosing the cancer early is essentially the only hope for cure. Smoking and family history are currently the only known risk factors for the disease, but ALISON P. KLEIN, M.D., director of the National Familial Pancreas Tumor Registry at Johns Hopkins, the world’s largest database on familial pancreatic cancer, is working to gain an even better understanding of what causes this lethal form of cancer. Her three-year plan is focused on identifying the key genetic alterations and environmental factors that start pancreatic cancer. Klein and colleagues could then develop prevention-based screening methods for those at high risk. This research also received CRF funding in 2005.

INTERCEPTING THE SIGNAL THAT TELLS ESOPHAGEAL CANCERS TO GROW
We now know that cancer is a genetic disease and are beginning to understand the specific changes that occur in cell checkpoints that cause cell signaling to run amok and lead to the unchecked cell growth that is the hallmark of cancer. Identifying the errors in these cell signaling pathways opens the door to correcting them with drugs that block errant signaling. Recent data indicates that over-expression of a gene known as EGFR results in a poorer outcome for patients with esophageal cancer. MICHAEL GIBSON, M.D., is conducting clinical trials combining the drugs gefitinib and cetuximab with chemotherapy and radiation therapy are underway to see if adding these drugs, which block EGFR expression, improve outcomes for patients with esophageal cancer that has begun to spread.

ALL CANCERS ARE NOT CREATED EQUALLY
All cancers are not the same. Classification of cancers is important for correct diagnosis and treatment. Currently, the best-defined models of cancer classification are in the leukemias and lymphomas in which discrete genetic changes have led to more specific diagnoses and successful therapies. SARAH J. WHEELAN, M.D., PH.D. and team are applying the same methodology to breast cancer by searching for additional molecular genetic markers to aid in diagnosis and treatment. They are particularly interested in an
aggressive and treatment-resistant subtype of breast cancer known as basal-like cancer. The work has allowed them to refine the characteristics of this breast cancer, and they are hopeful it will lead to a new cancer marker to improve early detection and treatment outcomes.

BREATHEING SHOULDN'T CAUSE A CANCER
A 2002 study of 500,000 adults found an 8 percent increase in lung cancer risk due to increased levels of ambient fine particulate matter. Ambient particulate matter is a general term used to describe a mixture of solid particles and liquid droplets in the air. It includes everything from smoke and fumes to dust and pollen. Fine particulate matter is formed from chemical reactions of particles in the air and is small enough to more significantly penetrate and cause harm to the respiratory system when it's breathed in, potentially contributing to diseases such as lung cancer. The Bloomberg School of Public Health was awarded a Science to Achieve Results grant (STAR) from the Environmental Protection Agency to form the Johns Hopkins Particulate Matter Research Group and study the health risks of particulate matter air pollution. Additional funding from the C.R.F. has given investigators, led by Allison Geyh, Ph.D., a unique opportunity to explore the causes of these health effects. Center investigators will combine detailed monitoring and particulate matter samples collected nationwide with analysis of national databases on air pollution, mortality, and hospitalization to determine the impact of exposure on pulmonary and cardiovascular diseases. The team is particularly interested in identifying elemental metals and metal-containing compounds in the air. It is known from occupational studies that some metal-containing compounds are toxic and associated with the development of cancer. Identifying such compounds in ambient particulate matter could, for the first time, provide a possible explanation for the linkage between ambient particulate matter and risk of lung cancer mortality.

HELP TO STOP SMOKING MAY HELP TO STOP CANCER
Smoking is the most preventable cause for death and disease in the United States. It increases the risk for lung and other cancers as well as cardiovascular and respiratory diseases. A nurse-run program directed by Robin P. Newhouse, Ph.D., R.N., is aiming to reduce lung cancer incidence and death rates in Maryland by improving the success of smoking cessation efforts for smokers discharged from acute-care hospitals. An inpatient nurse-delivered smoking cessation program will be tested with 150 patients. The study will compare standard education (written information, surveys, and a film on smoking cessation) with more intensive and individualized intervention, including a personal in-hospital smoking cessation counseling session by nurses. If the nurse-directed intervention is more successful at helping patients to quit smoking, support for a standardized program will be initiated at the state's acute-care hospitals.

LIVE LONG ENOUGH, AND YOU'LL GET CANCER
Cancer is a disease of aging, with the majority of cases occurring in people 65 and older. Clinical cancer research is not adequately representing cancer's most common victims, say experts. Patients with cancer are living longer and experiencing better quality of life as a result of advances in cancer care, but they say, this growing number of elderly cancer patients has been underrepresented in cancer clinical trials.

A newly established Geriatric Oncology Program at Bayview Medical Center, directed by Gary R. Shapiro, M.D., seeks to address this issue by initiating older-specific clinical trials, promoting older cancer patients' participation in clinical trials, understanding and overcoming barriers to their participation in clinical trials, and improving risk assessment for older patients to maximize treatment effectiveness without compromising quality of life.

MAKING CANCER CELLS DIE
Genetic aberrations that render cells incapable of executing cell death not only promote cancer, but also contribute to the resistance of cancers to anticancer agents. Unraveling mechanisms to unleash the cell death program in tumors that harbor such genetic changes could lead to effective therapeutic interventions against cancer. The research of Atul Bedi, M.D., has provided fundamental insights into the molecular mechanisms that underlie the dynamic balance between death signals and key determinants of tumor-cell survival. Based on these insights, he is developing and testing therapeutic strategies that are designed to activate death receptor signaling in conjunction with a blockade of key molecular determinants of tumor-cell survival. These studies provide a foundation for collaborative translational projects aimed against a broad range of cancers.
SAFER BUT MORE EFFECTIVE DRUG THERAPIES

The goal of drug therapy for cancer is to be as toxic as possible to the cancer cell while minimizing the toxicity to the normal cell. In recent years, investigators have found that combining drugs not only targets varied aspects of cancer cell behavior but also improves the independent action of each drug and the overall success of treatment. Yet this approach also complicates dosing calculations, requiring measurements of the toxicity and effectiveness of not one drug, but of several, while at the same time, determining how interactions between drugs impact on these measurements. Now, to identify and quantify drug synergies, a research team directed by Elizabeth Sugar, Ph.D., is developing a model to calculate the highest tolerable dose and also identify equally effective doses that may have lower toxic effects to normal cells.

TARGETING CANCER-PROMOTING CELL SIGNALS

Deciphering the complex process of cell signaling in cancer origination and progression is the focus of Michael Ochs, Ph.D. As more is understood about the proteins involved in transforming normal cells into cancer cells, clinicians and investigators have been able to pinpoint key signaling activity that could be targeted with cancer therapies. They will create a bioinformatics model of cell signaling networks to increase understanding of cancer and the signaling malfunctions that help it grow and spread, its response to treatment, and how it recovers from attacks by anticancer drugs. This model will, for the first time, allow investigators to simultaneously measure the activation state of multiple signaling proteins and the cell behavior correlated to this activity. This model will also help verify that new biologically-targeted drugs are actually hitting their targets.

UNCOVERING WHY SOME SMOKERS GET LUNG CANCER WHILE OTHERS DON'T

Cancer has been identified as a genetic disease. Still, understanding why environmental exposures cause genetic changes that make certain people susceptible to developing cancer while leaving others unscathed, has been a bit of a mystery. In lung cancer, cigarette smoke is a clear environmental factor, but why smoking leads to genetic changes that cause lung cancer in just 10 to 20 percent of smokers is largely unknown. Now, using advancing knowledge of the human genome and DNA samples from smokers in the Baltimore metro area, Shyam Biswal, Ph.D., and Paul Strickland, Ph.D., will perform whole-genome association studies using a newly developed technology called SNP (pronounced snip). SNP allows investigators to rapidly pinpoint differences in nucleotides (the cellular alphabet of ATCG that makes up the coding sequences of genes) among individuals and populations and help uncover novel genes and regions of susceptibility for cancer. Investigators will study smokers who have developed lung cancer and those who have not. Of specific interest will be African Americans, who have higher lung cancer death rates.

CRF INVESTIGATORS RECEIVING HONORS AND AWARDS

Science Watch, a newsletter published by Thomson Scientific names CRF investigators Stephen Baylin, M.D., James Herman, M.D., and David Sidransky, M.D. as best in their field, calling the Kimmel Cancer Center a cancer research powerhouse. With more than 90,000 references between them, the three, along with Kimmel Cancer Center researchers Bert Vogelstein, M.D., and Kenneth Kinzler, Ph.D., were named as the most frequently cited in cancer research from 1995-2005. Calling them, “doctors of the decade,” Science Watch editor Christopher King said, “The impressive number of citations these exceptional researchers have received is evidence of their profound influence on modern scientific thought.”

Anirban Maitra, M.B.B.S., has been awarded the Maryland Science Center’s 2006 Outstanding Young Scientist Award. Sponsored by the Maryland Academy of Sciences, the award includes the Allan C. Davis Medal and a cash award. Maitra’s laboratory is exploring the development of novel therapies for treating pancreatic cancer by identifying the genetic pathways causing the disease.

The Maryland Outstanding Young Scientist award program was established in 1959 to recognize the extraordinary contributions of young scientists in the state of Maryland. Many former recipients have gone on to distinguished careers in science.

Charles M. Rudin, M.D., Ph.D., associate professor of oncology, received a Barrow Group Welcomes Fred Clinical Scientist Award in Translational Research for his work on novel therapeutic strategies for small-cell lung cancer. The award supports the career development of U.S. and Canadian physician-scientists whose work bridges the gap between basic research and patient care.
“In the history of medicine, the greatest progress has been made in the application of biology to the behavior of humans through public health initiatives. Based on the biology of cancer, there is great potential to prevent the disease through lifestyle and medical interventions. The success of cancer research relies on a continuum, and prevention and control must be a part of it. Cancer research is not an either-or proposition. It is all interconnected.”

MARTIN D. ABELOFF
FORMER KIMMEL CANCER CENTER DIRECTOR AND CRF CO-DIRECTOR WHO PASSED AWAY FROM CANCER IN 2007
CRF Making Headlines in 2006

Cracking Genome Codes, Finding Unlikely Answers

THE MARYLAND CIGARETTE RESTITUTION FUNDS AT JOHNS HOPKINS

GENOME CRACKED FOR BREAST AND COLON CANCERS

Scientists have completed the first draft of the genetic code for breast and colon cancers. Their report, published on-line in Science Express, identifies close to 200 mutated genes, now linked to these cancers, most of which were not previously recognized as associated with tumor initiation, growth, spread or control.

Just as sequencing the human genome laid the groundwork for subsequent research in genetics, these data lay the foundation for decades of research on colon and breast cancers,” says CRF investigator VICTOR VELCULESCU, M.D., PH.D.

Although gene discoveries by independent scientists scattered around the world have provided clues, Velculescu says relatively few genes have been shown to be altered in cancers. The Hopkins gene hunters, which also included CRF investigator BEN PARK, M.D., say the number of gene that were altered in breast and colorectal cancer genomes surprised them.

These findings will guide and provide support for future comprehensive genetic studies including those envisioned by The Cancer Genome Atlas Project. Future research will include performing similar analyses on other tumors types, charting the pathways through which each mutant gene acts, and looking for common mutations that can be targeted with therapy.

GRILLING OUT: GOOD FOR THE TASTE BUDS BUT BAD FOR THE PROSTATE?

Men firing up their backyard grill may be getting an extra unwanted condiment with their mustard and ketchup, and it could lead to prostate cancer—namely 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine, or PhIP. The compound forms in meats cooked at very high temperatures, such as those cooked over flames.

Previous animal studies showed that rats fed food mixed with PhIP had more gene mutations and precancerous lesions in the ventral lobe located in the front of the prostate gland than rats not fed the compound. New data reported by the American Association of Cancer Research shows inflammation, a known contributor to development of many types of cancer, was also noted in the ventral lobes of the PhIP-fed rats, says study leader and CRF investigator ANGELO DEMARZO, M.D.

“For humans, the biggest problem is that it’s extremely difficult to tell how much PhIP you’ve ingested, since different amounts are formed depending on cooking conditions,” says study collaborator and CRF investigator WILLIAM NELSON, M.D., PH.D. “As a result, it has been difficult to fully determine how much human prostate or other cancers might be caused by PhIP.”
SOY’S CANCER PREVENTION PROPERTIES QUESTIONED

Johns Hopkins and Georgetown University researchers conducted a meta-analysis of 18 epidemiologic studies revealing that women who eat soy products may have a slightly lower risk of developing breast cancer. But the researchers quickly added that inconsistencies and limitations among the studies raised doubt about the potential benefits, and warned that high-dose supplements could do more harm than good. “At this point, women should not be taking high-dose soy supplements if they are breast cancer survivors or at increased risk for the disease,” says CRF investigator BRUCE TROCK, PH.D. “We don’t have long-term data on the effects of these supplements, and there is some evidence that they could be harmful.” Tests of refined soy products in animals revealed increased tumor growth, and short-term studies of women taking the supplements showed changes in breast cell growth that might actually increase risk for breast cancer.

Results of the review by Trock and his colleagues at Georgetown University, published in the April 5th issue of the Journal of the National Cancer Institute, found inconsistencies among the studies. Many differed in whether or not—or how— they accounted for the many factors that may impact development of breast cancer, such as body mass index (BMI). Studies that took BMI into account showed that soy had less of a protective effect than those that ignored BMI. “This is consistent with the idea that people who eat a lot of soy may eat fewer calorie-heavy foods and are less likely to have high BMI,” explains Trock. “This means that breast cancer risk may not be due to eating soy products, but to other dietary or lifestyle factors.”

After averaging results from the studies, which span a quarter century, researchers found that the overall relative reduction in breast cancer risk for soy breast cancer. “The important aspect is eating actual soy-based foods like tofu, not highly purified isoflavone supplements,” he adds. “Highly refined components of soy can have very different biological effects than eating tofu or drinking soymilk.” Instead of pill supplements, Trock suggests replacing some meats with soy foods such as tofu, soy milk or soy nuts for people who want to add soy to their diet.

BETTER MARKERS OF PROSTATE CANCER

A small but significant study focused on a protein called EPCA for early prostate cancer antigen. Blood tests for the marker predicted prostate cancer with 94 percent accuracy, compared to 25 to 30 percent accuracy for PSA. A larger trial of 600 men is now under way.

In other research, CRF investigators ANGELO DEMARZO, M.D., PH.D., and WILLIAM NELSON, M.D., PH.D., found that prostate cancer cells express lower levels of the protein GSTP1. They are now working on a test to measure GSTP1 levels in blood.

SECONDHAND SMOKE INCREASES CERVICAL CANCER RISK

CRF researchers ANTHONY ALBERG, PH.D., M.P.H., and CONNIE TRIMBLE, M.D., report that second-hand smoke increases a woman’s risk of cervical cancer. Their study of more than 50,000 women found that those who lived with smokers had a 40 percent or greater risk of developing cervical cancer.

UNLIKELY PROTEIN IMPLICATED IN PROSTATE CANCER

A quirky muscle protein known as myosin VI may help prostate cells evade cancers and help them stay that way. In laboratory studies of human prostate cancer cells, investigators, including CRF researcher ANELISA LOE, M.D., PH.D., found overproduction of myosin VI in prostate cancer cells and precancerous prostate lesions. When they altered the cells to shut down production of myosin VI, the cells lost some of their cancer characteristics.

Their results, published in the November 2006 American Journal of Pathology, suggested that myosin VI may be critical in starting and maintaining the malignant properties of the majority of human prostate cancers diagnosed today. The investigators found that among 59 samples of benign and cancerous prostate tissue, myosin VI expression was almost four times higher in prostate cancer samples than in normal prostate tissue samples. What’s more, they found that overproduction of the protein occurs early in cancer development, including common precursor prostate disorders known as PIN (prostatic intraepithelial neoplasia) and PIA (proliferative inflammatory atrophy).

DeMarzo says, “Creating a laboratory test to identify high or low levels of myosin VI in urine or blood might aid in the early detection of prostate cancer.”

KEY TO LUNG CANCER CHEMOTHERAPY RESISTANCE REVEALED

Investigators led by CRF researcher SHYAM BISWAL, PH.D., discovered how taking the brakes off a “detox” gene causes chemotherapy resistance in a common form of lung cancer. Products made by a gene called NRF2 normally protect cells from environmental pollutants like cigarette smoke and diesel exhaust by absorbing the materials and pumping them out of the cell. Another gene called KEAP1 encodes products that stop this cleansing process. But lung cancer cells sabotage the expression of these same genes to block assault from chemotherapy drugs.

“What we’re seeing is that lung cancer cells recruit and distort NRF2 and KEAP1 expression to help tumor cells evade the toxic effects of chemotherapy,” Biswal says. He and colleagues published results of cell culture studies in the October 3, 2006, issue of PLoS Medicine.
A CLOSER LOOK

Prostate Cancer Test

RESEARCH
While the PSA (prostate specific antigen) test has led to earlier detection of prostate cancers, the test also has a high rate of false positive results.

TRANSLATION
DR. WILLIAM NELSON and team discovered the most common genome alteration in prostate cancer. They developed a biomarker test that can be used in conjunction with PSA to detect precancerous changes and prostate cancer.

APPLICATION
Johnson & Johnson has licensed the test making mass distribution and broad-based use possible.
MAKING THE CONNECTION: RESEARCH TRANSLATION APPLICATION CRF INVESTIGATOR WILLIAM NELSON
Edward Burns learned about CRF-sponsored free prostate cancer screenings three years ago when he was chatting with friends. Another friend had died from prostate cancer, and Burns decided to get screened. He has done so every year since. “These screenings are so important,” says Burns. “There are a lot of people who don’t have insurance and can’t afford to pay to see a doctor.”
2007
By the Numbers

7 Targeted Cancers:
  Breast cancer
  Cervical cancer
  Colorectal cancer
  Lung cancer
  Melanoma skin cancer
  Oral cancer
  Prostate cancer

Research:
$2.47 million research dollars awarded
5 faculty members recruited
10 translational research awards

Prostate Cancer Prevention, Education, Screening and Treatment:
$1.2 million public health grant awarded
104,000 people reached through media
6,750 people educated
501 people screened
6 men diagnosed and treated for prostate cancer
A STRATEGY FOR REDUCING BREAST CANCER DISPARITIES

Breast cancer is a leading cause of cancer death in Maryland and throughout the U.S. These mortality rates are even more striking among African-American women, who are often diagnosed with more advanced stages of disease, and so often don’t do as well as their Caucasian counterparts. "A shift to earlier diagnosis would then be a logical step toward a reduction in cancer mortality and, potentially, a reduction in existing racial disparities in cancer mortality," says JEAN FORD, M.D., director of the CRF Public Health Grant. He began a pilot study to explore whether removing barriers to cancer detection and treatment will improve outcomes for minority women with breast cancer.

Research has indicated that African Americans receive less intensive therapies and experience shorter survival time. Ford says it is interesting to note that in Baltimore City, Caucasian and African-American women have comparable breast cancer death rates. This, Ford says, is probably because both these groups are likely to have low incomes that limit their access to care, and it provides further anecdotal evidence that delayed detection and treatment may be at the root of the poor outcomes for minority women.

Ford proposed a strategy using nurse-led community healthcare workers, called patient navigators, to work with low-income, uninsured women in Baltimore City who are 40 or older and at average or increased risk for breast cancer due to personal or family history. Navigators will provide culturally-tailored educational materials adapted with literacy and age-related factors, such as vision and hearing, in mind. Navigators will assist women with scheduling screening and treatment appointments.

THE MARYLAND CIGARETTE RESTITUTION FUNDS AT JOHNS HOPKINS

2007 RESEARCH AWARDS

FORMER KIMMEL CANCER CENTER DIRECTOR and CRF co-director Martin D. Abeloff said, “In the history of medicine, the greatest progress has been made in the application of biology to the behavior of humans through public health initiatives. Based on the biology of cancer, there is great potential to prevent the disease through lifestyle and medical interventions. The success of cancer research relies on a continuum, and prevention and control must be a part of it. Cancer research is not an either-or proposition. It is all interconnected.”

On September 14, 2007, Dr. Abeloff lost his life to the disease he had dedicated his life to fighting. Under his leadership, some of the most salient findings in cancer genetics and cancer cell biology were realized and have begun to be translated into patient care.
arranging transportation, and even accompanying women to appointments, if necessary. The initial study will involve 250 women to determine if the participation of navigators leads to increased screening, access to prompt and appropriate therapies, and proper follow-up care with the ultimate long-term goal of improving survival rates for African-American women in Baltimore City.

PATIENT NAVIGATION ELECTRONIC LOG
Preliminary data from the prostate cancer screening program suggest that community healthcare workers are helpful to patients in coordinating cancer screening and followup. However, few tools are available to assist them in delivering interventions tailored specifically to patient needs. In collaboration with investigators at the University of Maryland, Jean Ford, M.D., and team have developed a Patient Navigation Electronic Log (PaNEL), a computerized system designed to guide community healthcare workers. The new system provides them with strategies to determine patient needs, and improve coordination of prostate cancer screening while reducing barriers to care.

IN LUNG CANCER, SMALL CELL EQUALS BIG PROBLEM
Lung cancer tops all other cancers in terms of the number of lives it claims. Small cell lung cancer represents 15 percent of all lung cancers and occurs almost exclusively in smokers. While up to 85 percent of patients' cancers initially respond to anticancer drugs, almost all patients die of recurrent disease within one year of diagnosis. This has been the case for nearly two decades underscoring the critical need for new therapies.

CHRISTINE HANN, PH.D., studied a gene called Bcl-2 that inhibits cell death and is overexpressed in the majority of small cell lung cancer cases. Abnormal expression of this protein has been linked to therapy resistance, making it a promising target for new therapies. Hann and collaborators studied a drug that directly inhibits Bcl-2, which has proven effective in laboratory models. Clinical trials of this drug and other combination approaches of Bcl-2 inhibitors and anti-cancer agents are now underway at Johns Hopkins. Hann also is studying cancer stem cells, an extremely small but lethal population of cells within tumors. Such populations have already been identified in several solid tumors, including breast and prostate cancers, and are thought to play a role in therapy resistance and tumor recurrence. Hann and team are using the Bcl-2 inhibitor in prediagnostic studies to try to uncover lung cancer stem cells. They hope that the inhibitors, which successfully kill the bulk of the tumor, will help them reveal and define the rare treatment-resistant cancer stem cells hiding within lung cancers.

NEW CANCER THERAPIES
Clinical trials are the mechanism by which research institutions like Johns Hopkins move promising new therapies from the laboratory to the bedside and confirm their safety and effectiveness. Recent studies of NCI-sponsored trials indicate that more than half of children diagnosed with cancer participate in clinical trials, regardless of race, ethnicity, or socioeconomic status. By contrast, only two to three percent of adults with cancer enter clinical trials, and minorities and low-income patients are often underrepresented.

Improving Participation in Oncology Research Trials (IMPORT) is a pilot study led by Mollie Howerton, Ph.D., aimed at pinpointing specific factors that keep patients from participating in clinical trials. The research team will interview 102 patients, half of them African-American and half Caucasian, to better understand how patients make decisions about clinical trials. The research team will explore awareness of trials, geographic proximity to trial sites, income and insurance status, social and cultural dynamics, and other factors to better determine what patients know about clinical trials and barriers that hinder participation.

UNCOVERING "SICK" COMMUNITIES
Evidence has long supported that many cancers originate because of where we are, not who we are. It is true that cancer is a genetic disease, but investigators are now asking where those bad genes come from. While it is clear that many of them come from behaviors such as cigarette smoking and poor and unbalanced diets; others are likely related to things outside of our direct control. There is evidence that people who live in communities close to highways and other high-traffic areas are exposed to airborne toxins that contribute to cancer and respiratory diseases. Investigators led by Norma Kanarek, Ph.D., studied Maryland communities in an effort to reveal environmental factors, such as air quality, that contribute to cancer development. They believe well-being may be synonymous with positive demographics that have been traditionally associated with better health, including higher education, income, white race, and home or car ownership are some of these factors, and they can be associated with individuals and communities.

CANCER AND DIET
A CRF Research Matter collaborative grant between Maureen Black of the University of Maryland and Ann Klassen, Ph.D., of Medicine was used to study the impact of obesity on cancer. Experts report that 20 percent to 50 percent of fatal cancers are attributable to poor diet. Black and Klassen established a life span approach to reducing cancer-related dietary risk in low-income families. They used information, including 24-hour diet records and food frequencies, from 1,300 infants, children, adolescents, and adults to identify determinants of diet and behavior associated with cancer risk. The researchers looked for risk factors for being overweight and rapid weight gain and ways to reduce these risks. The data was used to obtain additional grants for intervention studies.
Investigators have developed a risk “calculator” for one of the most lethal forms of cancer. A novel computer software tool described in the April 10, 2007, Journal of Clinical Oncology, will help identify people at risk of developing pancreatic cancer due to an inherited genetic predisposition.

Physicians and genetic counselors can use the tool to decide who would benefit from early screening. The calculator, called PancPRO, computes the chance that a person carries a pancreas cancer gene and his or her lifetime risk of developing the disease. It is based on similar tools used in breast and colon cancer risk assessment.

An estimated 10 percent of pancreas cancers are caused by inherited gene alterations. “Even if there is a 100 percent chance that an individual carries a pancreas cancer gene, the person’s lifetime risk for developing the disease is only 32 percent by age 85,” says CRF investigator ALISON KLEIN, PH.D.

Pancreas cancer is often diagnosed after it has spread, leading to very low survival rates and making early risk assessment key to improving outcomes. Though researchers don’t yet know specific genes that cause the disease, Klein says their understanding of how genes behave coupled with information about a family, such as age, family size and causes of death, mean that her model can provide a good estimate of an individual’s risk.

Klein and team tested the software with data collected from about 6,000 people from 961 families when the registry was established more than a decade ago. They compared PancPRO predictions with actual occurrence of pancreas cancer in these families over an 11-year period. PancPRO predicted that 31 of the registry participants would develop cancer, just slightly higher than the 26 who actually did.
and IPF,” said CRF investigator Armanios, “it may lead us to a better understanding of the genetic properties causing more common forms of the disease.”

Investigators have developed a risk “calculator” that will help identify people at risk of developing pancreatic cancer (one of the most lethal forms of cancer), due to an inherited genetic predisposition.

In cancer, it may be wise to make mountains out of molehills. “The special genetic landscape of a cancer cell can get to cancer cells. In essence, the NRF2 gene directs proteins to absorb pollutants and pump them out, clearing cells of toxins. Another gene, KEAP1, he says, lets cells know when the toxins are removed, shutting down NRF2 and stopping the cell-cleansing process.

In Biswal’s study, six of 12 lung cancer cell lines and 10 of 54 tissue samples from non-small cell lung cancer patients had mutations in the KEAP1 gene, rendering it inactive and unable to keep NRF2 activity in check. In addition, half of the tissue samples were missing one copy of the KEAP1 gene (cells usually have two copies of each gene). No missing genes or mutations were observed in normal lung tissues from the same patients.

Biswal believes that blocking NRF2 expression in lung cancer patients receiving chemotherapy could improve the effectiveness of the drug therapy. He plans to confirm the findings with a set of samples and screen for drugs that block the gene.

The research team is now looking for pathways that these varied genes have in common. “The hard part used to be finding these mutant genes,” says Velculescu. “Now the challenge will be to link them to specific pathways and understand their function.” They say it is possible to expect to see a similar genetic landscape—few mountains surrounded by many hills—in other cancers.

LUNG CANCER USES CELL DETOXIFIER TO EVADE ANTICANCER DRUG

On any given day, our bodies are assaulted by a number of environmental pollutants—cigarette smoke, diesel exhaust, carbon monoxide and more. But the same processes our body uses to protect itself from outside assaults have been corrupted by lung cancer cells to help them evade anticancer drugs.

CRF investigator Shyam Biswal, Ph.D., is the leading expert on a gene called NRF2 that protects our cells from these pollutants. He found that NRF2 directs proteins to absorb pollutants and chemicals and then pump them out before they can get to cancer cells. In essence, the lung cancer cells shut down KEAP1, which leaves the NRF2-directed cell cleansing mechanism continually activated, sweeping anticancer drugs away with other cell toxins before they can do their job against cancer cells.

In Biswal’s study, six of 12 lung cancer cell lines and 10 of 54 tissue samples from non-small cell lung cancer patients had mutations in the KEAP1 gene, rendering it inactive and unable to keep NRF2 activity in check. In addition, half of the tissue samples were missing one copy of the KEAP1 gene (cells usually have two copies of each gene). No missing genes or mutations were observed in normal lung tissues from the same patients.

Biswal believes that blocking NRF2 expression in lung cancer patients receiving chemotherapy could improve the effectiveness of the drug therapy. He plans to confirm the findings with a set of samples and screen for drugs that block the gene.
THE MARYLAND CIGARETTE RESTITUTION FUNDS AT JOHNS HOPKINS

(LEFT TO RIGHT) STEPHEN BAYLIN, JAMES HERMAN, AND MALCOLM BROCK
Brain Cancer

RESEARCH
Brain cancer is among the deadliest of all cancers. The most common form of brain cancer is glioblastoma multiforme and the most lethal, with most patients surviving just 14 months from diagnosis.

TRANSLATION
Johns Hopkins Kimmel Cancer Center researchers linked the MGMT gene to glioblastoma multiforme. The investigators discovered the gene was altered by a cellular process known as hypermethylation. They discovered that the gene alteration makes brain cancer cells more responsive to anticancer drugs known as alkylating agents. The technology is licensed by OnoMethylome Sciences.

APPLICATION
OnoMethylome Sciences gives a commercial license to LabCorp for a MGMT methylation test available to patients throughout North America.

Leukemia

RESEARCH
Myelodysplastic syndrome is a preleukemic, potentially deadly disease not well understood outside of the academic research hospital setting.

TRANSLATION
Pioneering laboratory research by CRF investigators Stephen Baylin, M.D., and James Herman, M.D., revealed alterations in a cellular process known as DNA methylation. Key tumor suppressor genes were found to be turned off by too much DNA methylation. This process has been linked to MDS and a host of cancers. The work was honored in 2004 with the most outstanding research award in the National Cancer Institute's SPORE (Specialized Programs of Research Excellence) program.

APPLICATION
Clinical trials of the drug 5-aza-cytidine that blocks methylation and restores the function of tumor suppressor genes have led to complete remissions in up to half of MDS and leukemia patients treated. Results from multicenter trials led to the first FDA approval of a demethylating agent.
Baltimore resident Dante Mendoza visited the Hispanic Apostolate, a Johns Hopkins community partner, where he received his first ever prostate exam. Two years later, Mendoza received a reminder letter telling him it was time for his annual exam. He scheduled an appointment for a free prostate cancer screening jointly offered by the Johns Hopkins Kimmel Cancer Center and Alvin and Lois Lapidus Cancer Institute at Sinai Hospital. This time the results were different. He learned he had prostate cancer. Six months later, he underwent prostate cancer surgery at Johns Hopkins. “Everything is fine now,” says Mendoza who says he is cancer-free.
2008

By the Numbers

7 Targeted Cancers:
Breast cancer
Cervical cancer
Colorectal cancer
Lung cancer
Melanoma skin cancer
Oral cancer
Prostate cancer

Research:
$2.15 million research dollars awarded
2 faculty members recruited
1 faculty retained
7 translational research awards

Prostate Cancer Prevention, Education, Screening and Treatment:
$1.2 million public health grant awarded
2,652,639 people reached through media
12,671 people educated
730 people screened
8 men diagnosed and treated for prostate cancer
A Personalized Colon Cancer Test

RESEARCH
Colon cancer is curable nearly all of the time if it is detected early. While colonoscopy is effective at detecting early cancer, it is an invasive test with some risks, and therefore, people often do not take advantage of the test.

TRANSLATION
CRF investigator Luis Diaz, M.D., has developed a simple, inexpensive blood test that detects fragments of DNA shed by colon cancer cells into the bloodstream. The test not only detects the presence of tumor, but tracks its progress.

APPLICATION
The test is currently being tested in colon cancer patients. Once proven, it can be used to detect the DNA of virtually all solid tumors.

Ushering in the era of personalized medicine, this test should save both lives and money by helping clinicians separate those patients who need additional tests and procedures from those who do not as well as distinguishing those who will benefit from adjuvant chemotherapy from those who do not need additional treatment.
CANCER-EATING BACTERIA
LUIS DIAZ, M.D., received a diversity grant to support his studies of the bacteriolytic cancer therapy Clostridium novyi–NT. The genetically modified bacteria destroys cancer cells in the oxygen-starved core of tumors but shows no interest in tissues not harboring cancers. A single intravenous injection of the bacteria spores was successful in animal models, destroying tumors up to 30 percent of the time. Clinical trials in patients with metastatic colon tumors have since begun.

SMOKING-RELATED CANCER PATTERNS
Earlier studies have suggested there may be a common genetic predisposition to all smoking-related cancers. In this new study, hermANN ARTHUR BEATY, M.D., ALISON KLEIN, PH.D., and LI WANG, PH.D., will use data collected from the National Familial Pancreas Tumor Registry at Johns Hopkins to determine if cancers other than pancreatic cancer occur at a greater rate than expected among these families and to look for clusters of smoking-related cancers.

EPIGENETICS CORE LAB FACILITY
Epigenetics is a powerful clinical tool to improve the diagnosis, prognosis, and treatment of cancer patients and is moving ever closer to clinical reality. Recent technical advances like MSP (methylation specific polymerase chain reaction) can now be used to determine if genes are hypermethylated, the hallmark of epigenetic alterations that can lead to the silencing of key tumor suppressor genes. An Epigenetics Core Laboratory, directed by MALCOLM BROCK, M.D., would make state-of-the-art DNA methylation analysis available to Cytogenetists, and eventually to investigators throughout Johns Hopkins, ensuring accurate and reliable DNA methylation laboratory results.

THE LINK BETWEEN CHRONIC INFLAMMATION AND ESOPHAGEAL AND LUNG CANCERS
Esophageal and lung cancers develop through progressive molecular events that include epigenetic alterations, or alterations to genes that occur without actually mutating the DNA. These epigenetic alterations may result from environmental exposures as well as inflammation, and epigenetic expert JAMES HERMAN, M.D., believes they are among the first events in the development of these cancers. Herman will use animal models to determine if environmental exposures produce a chronic state of inflammation, leading to epigenetic alterations that ultimately result in cancer.

DECIPHERING LUNG CANCER RESISTANCE
Shyam Biswal, Ph.D., will perform a systematic metabolic profile of lung cancer cells with a deregulated Nrf2 gene and pathway to help gain an understanding of how it causes lung cancer cells to become resistant to therapy. Biswal, working with GEFFREY GUMIN from University of Maryland, began screening 1280 compounds that can knock down Nrf2 in patients. The best candidate will be used in lung cancer patients to block resistance to chemotherapy.

MODEL FOR QUALITY CARE
The highest quality care leading to the best patient outcomes depends on well-defined and available indicators, knowledge of institutional performance, and analysis that sheds light on the quality improvement process. This project, led by NORMA KANAREK, PH.D., incorporates a collaboration of clinicians treating the most prevalent cancers—prostate, breast, colorectal, and lung cancers—and an epidemiologist to prioritize indicators from the Johns Hopkins Hospital Cancer Registry and assemble a multi-year database of Johns Hopkins Kimmel Cancer Center patient demographics and care patterns. Lessons learned from these common cancers will also be applied to less common cancers. This method will help highlight quality care, enhance clinical trial access, and identify the key factors in achieving the best cancer outcomes.

INFLAMMATION AND METHYLATION AS PROSTATE CANCER PREDICTORS
CRF investigators ELIZABETH PLATZ, M.P.H., SC.D., SRINIVASAN YEGNASUBRAMANIAN, M.D., PH.D., ANGELO DEMARZO, M.D., PH.D., WILLIAM NELSON, M.D., PH.D., and CHARLES DRAKE, M.D., PH.D., believe that hypermethylation (increased methylation to genes that can ultimately silence key tumor suppressor genes) and inflammation caused by environmental insults conspire to influence the early stages of prostate cancer. The investigators will use a multi-faceted approach to determine whether environmental exposures influence hypermethylation, leading to chronic inflammation inside the prostate gland and if, jointly, they increase the risk of prostate cancer.

HORMONES AND BREAST CANCER
AC1 female rats develop mammary cancers within 12-14 weeks following treatment with estradiol, an estrogen. This animal model is receiving increasing attention as a way to determine the mechanisms of human breast cancer development associated with aromatic metabolic profiles of liver cancer cells with a deregulated Nrf2 gene and pathway to help gain an understanding of how it causes lung cancer cells to become resistant to therapy. Biswal, working with GUMIN from University of Maryland, began screening 1280 compounds that can knock down Nrf2 in patients. The best candidate will be used in lung cancer patients to block resistance to chemotherapy.

GI CANCER PROGRAM DEVELOPMENT
NILOFER AZAD, M.D., is a clinician-scientist specializing in colorectal and other GI cancers. She recently completed a four-year fellowship in medical oncology at the National Cancer Institute (NCI). At the NCI, Azad worked with the leader of the Phase I Drug Development Group, giving her the skills to develop her own phase I/II drug development program in GI oncology.

SMOKING CAUSES CANCER, BUT NOT IN EVERYONE
While more than 80 percent of chronic obstructive pulmonary disease (COPD) and lung cancer patients are smokers, only 15-20 percent of smokers get COPD and only 10-15 percent of smokers get lung cancer. Shyam Biswal, Ph.D., plans to find out why and use it to help uncover the body’s own defense mechanisms against environmental triggers and identify those genetically predisposed to smoking-related diseases, such as lung cancer. Because the genetic factors that contribute to susceptibility are largely unknown, he continues to sift through candidate genes. It is breakthrough study in 2002 showed that activation of a gene, Nrf2, can turn on antioxidant genes. Using this paradigm for investigating cigarette smoke effects on lungs and genes, Biswal’s research is now focused on enumerating the genes controlled by Nrf2 and their role in causing disease. Next he will conduct a whole-genome assay for multipletenic influences of Nrf2, in search of ways to fight drug resistance and oxidative cell damage, and to mitigate damage caused by cigarette smoke and other environmental factors.
According to State statistics, there are 40,000 uninsured African American men in Baltimore City. “We don’t care where they are,” says Ndi. “We just want to get to them.”
CHARLENE NDI HAS spent her entire career reaching out to the poor and underserved to bring them vital healthcare. She is undeterred by the challenge of bringing humanness to discussions of this often faceless population. Still, there is a practicality and deliberateness about her that makes one immediately understand that she not only cares about this immensely difficult problem, but she can help solve it as well.

And, do not be mistaken, it is a monumental task before her and her team, one that can at times seem insurmountable. As Program Manager for the Maryland Cigarette Restitution Fund’s Public Health Grant at Johns Hopkins, she and her team are charged with bringing prostate cancer screening to uninsured African American men, age 45-70, who live in Baltimore City. The city has some of the highest prostate cancer death rates in the nation, and African American men suffer disproportionately to their Caucasian counterparts. State legislators are hopeful the CRF-sponsored screening program, which began in 2001, will lead to earlier detection of prostate cancer and, as a result, better treatment outcomes for African American men, and over time, an improvement in the city’s prostate cancer death rates.

NDI has only been at Johns Hopkins’ Kimmel Cancer Center’s Cancer Disparities Program since March, but under her brief management, the program achieved a screening milestone—a record 718 men were screened in 2008.

This year, the program’s goal is 900, but she will have help through a new partnership with the Baltimore City Health Department and Sinai Hospital, HealthCare for the Homeless, and the Maryland Center for Veterans Education and Training, so that they can make inroads to these communities for colon cancer screening. Since 2006, the Cancer Disparities Program has coordinated screening of underserved men and women for colon cancer through a subcontract from a Center for Disease Control grant to the Johns Hopkins University. The infrastructure for screening for this cancer was already in place. Working with the Baltimore City Health Department and Sinai Hospital, they hope to screen at least 50 men and women through a CRF-supported initiative this year.

NDI’s group was on hand for prostate cancer screenings. Though 500 men were registered for the conference, most of the 82 men screened during the conference were not registered participants. They walked in off of the street to see what the event was about and decided to be screened.

As Ndi continues to face and meet the challenges of prostate cancer screening, she and her team also have begun making inroads to these communities for colon cancer screening. Since 2006, the Cancer Disparities Program has coordinated screening of underserved men and women for colon cancer through a subcontract from a Center for Disease Control grant to the Johns Hopkins University. The infrastructure for screening for this cancer was already in place. Working with the Baltimore City Health Department and Sinai Hospital, they hope to screen at least 50 men and women through a CRF-supported initiative this year.

According to Dr. Jean Ford, Director of the CRF Public Health Grant, “Charlene presents the unique blend of qualities that this program needs: management experience, in-depth knowledge of our small city, and a commitment to improving its health.”

Despite the difficulty of the task before her, Ndi remains optimistic. “What we are trying to do speaks to everything I have done for over the last 30 years,” says Ndi. “I love this job.”
Winning the Battles, but the War on Cancer Continues

BEYOND THE MICROSCOPE

Investigators Malcolm Brock and James Herman have uncovered a molecular trail of evidence left behind by lung cancer cells. This molecular evidence, invisible to the human eye and microscope, can tell clinicians that tumor cells remain after therapy and if they are likely to result in a cancer recurrence. Their findings were reported in the March 12, 2008, issue of the New England Journal of Medicine.

“[This is DNA] forensic for cancer,” says cancer surgeon and CRF investigator Malcolm Brock, M.D. “While there may be no visible trace of cancer after surgery, DNA evidence of tumor cells is left at the scene, hiding in tissues, such as lymph nodes.” And, they warn not to be fooled by size. While we have become accustomed to associating tumor size at diagnosis as an indicator of recurrence, Brock says, tiny tumors, even those as small as a pea, can harbor molecular genetic alterations that make them more aggressive.

Brock believes these findings will lead to new therapies for lung cancer, the leading cancer killer.

RESEARCH INDICATES NEED FOR EFFECTIVE HPV VACCINE FOR WOMEN AND MEN AND A SIMPLE HPV SCREENING TEST

A call to explore a broader use of HPV (human papillomavirus) vaccines and the validation of a simple oral screening test for HPV-caused oral cancers are reported in two studies by a Johns Hopkins Kimmel Cancer Center investigator.

Leading HPV expert and CRF investigator Maura Gillison, M.D., Ph.D., the first to identify HPV infection as the cause of certain oral cancers and who identified multiple sex partners as the most important risk factor for these cancers, reports her latest work in the November 15, 2008, supplement edition of Cancer.

In the CDC report, believed to be the first and most comprehensive assessment of HPV-associated cancer data in the United States, investigators analyzed cancer registry data from 1998-2003. Gillison and team found approximately 20,000 cases of cancer in the United States each year are caused by HPV infection. Oral cancers are the second most common type of HPV-associated cancers and are increasing in incidence in the U.S., particularly among men. Add to that anal, penile, vaginal, and vulvar cancers that are also linked to HPV infection, and Gillison says these cancers, when combined, equal the number of cervical cancers, the most common and well known of the cancers caused by HPV.

While about one-quarter of HPV-linked cancers occur in men, vaccines are currently approved only for use in girls and young women for cervical cancer prevention. “We need to have a more comprehensive discussion of the potential impact the HPV vaccine could have on cancer rates among men and women in this country,” says Gillison, associate professor of oncology.

Currently available HPV vaccines have the potential to reduce the rates of HPV-associated cancers, like oral and anal cancers, that are currently on the rise and for which there are currently no effective or widely-applied screening programs. Gillison notes, however, that studies are needed to confirm that the vaccine effectively reduces HPV infections that lead to oral and anal cancers.

Other than prevention, early detection is held by cancer experts as the best way to control cancer. In the Clinic Cancer Research study, the first to track the disease and related oral infections over an extended period, Gillison found that simple “swish and spit” oral rinses can successfully track oral HPV infection over time. The findings open the door to a potential, non-invasive screening test to detect the disease and monitor for tumor recurrence.

COMPREHENSIVE GENETIC BLUEPRINTS REVEALED FOR LETHAL PANCREATIC, BRAIN Cancers

The researchers who, with the help of CRF support, completed the maps of the breast cancer and colon cancer genomes in 2007, has now used the same principles to complete the genetic blueprint for lethal pancreatic and brain cancers. The latest findings were reported in the Sept. 5, 2008, issue of Science Express.

Believed to be the most comprehensive result to date for any tumor type, the new map evaluated mutations in virtually all known human protein-encoding genes, comprised of more than 20,000 genes, in 24 pancreatic cancers and 22 brain cancers. A core set of regulatory gene processes and pathways, about a dozen for each tumor type, were found to be altered in the majority of tumors studied by the researchers. In pancreatic cancer, these 12 pathways, including those linked to DNA damage control, cell maturation, and tumor invasion, were altered in 67 percent to 100 percent of tumors.

“The perspective changes the way we think about solid tumors and their management, because drugs or other agents that target the physiologic effects of these pathways, rather than individual gene components, are likely to be the most useful approach for developing new therapies,” says CRF investigator Victor Velculescu, M.D., Ph.D.
2001-2008
A Review of the C RF

7 Targeted Cancers:
- Breast cancer
- Cervical cancer
- Colorectal cancer
- Lung cancer
- Melanoma skin cancer
- Oral cancer
- Prostate cancer

Research:
$19.67 million research dollars awarded for 131 research projects
47 faculty members recruited
24 faculty retained

Prostate Cancer Prevention, Education, Screening and Treatment:
$10.2 million awarded for public health grant
5,013,308 people reached through media
76,273 people educated
3,646 people screened
37 men diagnosed and treated for prostate cancer
2001–2008

CRF Award Recipients

Abdolli, Martin and Groisman, John
FY04 and FY05
Cancer Prevention and Control at SKCCC

Albargh, Anthony
FY01
The Joint Influence of Active and Passive Smoking on Cancer Incidence: A Long-Term Prospective, Cohort Study

Armstead, Mary
FY05 and FY07
Faculty Recruitment Grant
Long Term Consequences of Telomere Shortening and Telomerase Inhibition

Baylin, Stephen B., and Herman, James G.
FY02
Studies of risk assessment for, and the prevention of lung cancer

Beatty, Terry; Klein, Alison; and Li Wang
FY08
Mortality patterns due to smoking related cancers in families drawn from the national familial pancreatic tumor registry

Bedi, Atul
FY06
Activation of Death Receptor Signaling in Conjunction with Tumor-cell Survival

Biswal, Shyam
Funded: FY01 and FY03
Chemoprevention and biomarker discovery for cigarette smoke induced lung cancer

FY04
Proteomics Approach for Developing Biomarkers for N/V2 Cancer Chemoprevention

FY08 (joint Project with University of Maryland)
N/V2-dependent crostal of metabolic control and chlormalence in lung cancer

Biswal, Shyam S. and Streickland, Paul
FY06
Whole Genome Association Scans for Determining Susceptibility to Lung Cancer

Translation Research

Borzekowski, Dina L.G.
FY03
Adolescent anti-smoking messages, and the Internet

FY03
Smoking Cessation for Youth: A Comparison of Internet Based and School Based Interventions

Translation Research

Bower, Jamie V.
FY02
Promoting cancer prevention & control in Baltimore's African American Faith-Based Community

Brahm, Julie R.
FY01
Development of Strategies for the Prevention of Lung Cancer

FY05
HELP: The Hopkins Early Lung Cancer Prevention Program

Brahm, Julie and Rudin, Charles
FY03
Lung Cancer Discovery to Clinical Trial Translation (I and II)

Faculty Recruitment

Brok, Malcolm
FY08
Epigenetic CORE lab facility

Buckley, Timothy J. and Thomas A. Burke
FY01
Cancer Prevention in Maryland through Risk Characterization

FY03
Cancer Prevention in Maryland through Risk Characterization

Translation Research

Buckley, Timothy
FY03
Exposure Assessment: At the Crossroads of Environment, Cancer, and Prevention

Translation Research

Castano, Joseph
FY01
Molecular Screening in a Population at Risk for Head and Neck Cancer

Corecchi, Michael A.
FY02 and FY03
Drug development strategies facilitating the initiation and continuation of chemoprevention trials for solid tumor malignancies

Faculty Retention

Cruz-Correa, Marcia
FY01
Epidemiology of Loss of Imprinting in Colorectal Cancer in MD

Curless, Barbara
FY01
Lung Cancer in Women: Improved Understanding of Cancer Risk Factors

Faculty Recruitment

Drake, Charles G.
FY02 and FY03
Immunological studies for prostate cancer

Faculty Recruitment

Emens, Leisha A.
FY02
Timed sequential therapy with cyclophosphamide, doxorubicin, and a breast cancer vaccine

Faculty Recruitment

Translation Research

Erlinger, Thomas P.
FY02 and FY04
Inflammation and the risk of colon cancer

Colorectal Cancer in MD

Evaluation of Breast Ductal Lavage as an Adjunct to Mammography

Pilot Study

Faculty Retention

FY04
Setting Priorities for Implementing the 2003 Maryland Cancer Control Plan: An Evidence-based Approach

Herman, James
FY08
Epigenetic changes in preinvasive lung and esophageal neoplasia in the setting of chronic inflammatory changes

Howerton, Molly
FY05
Improving Minority Participation to Oncology Research Trials (IMPORT)

FY07
Barriers to participation of underrepresented populations in cancer-related trials

Translation Research

Jeon, Hee-Soon
FY01
Cancer Educational Program for Korean American Women: Pilot Study

Kanazaki, Norma
FY05
Traffic-related Air Pollution Exposures and Cancer Incidence in Maryland

Translation Research

FY08
Connections to Care and Outcomes at SKCCC

Khan, Soaad R
FY01 and FY02
Novel Drug Development for Solid Tumors

Haldon, Rolf
FY04
Human Fetal Exposure to Drinking Water Carcinogens in Maryland

Haldon, Rolf and Buckley, Timothy
FY04
Human Fetal Exposure to Drinking Water Carcinogens in Maryland

Huraki, Lesly A.
FY04
The N-terminal Mechanism of DNA Repair by KU Dependent Non-Homologous End Joining in Mammals: A Target for Anticancer Agents

Hans, Christine
FY07
Developing novel therapeutics for small cell lung cancer

Faculty Recruitment

Hibbs, Kathy J.
FY01
Evaluation of Breast Ductal Lavage as an Adjunct to Mammography

Pilot Study

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Translation Research

FY08
Connections to Care and Outcomes at SKCCC

Khan, Soaad R
FY01 and FY02
Novel Drug Development for Solid Tumors
Kim, Miyong  
FY02  
Developing and testing a multi-level community-based smoking cessation intervention program for Korean American Community in Maryland  
Faculty Retention  
Translational Research

Kim, Kristina  
FY02  
Race Disparities Among Cervical Cancer Patients  
Faculty Recruitment

Klassen, Ann C.  
FY07  
Using Lifestyle Segmentation Data to Understand Cancer Burden in Maryland  
FY07 (joint project with University of Maryland)  
From Infancy to Adulthood: A LifeSpan Approach to Reducing Cancer-Related Dietary Risk in Low Income Families

Klein, Alison  
FY05 and FY06  
Epidemiology of Pancreatic Cancer  
Faculty Recruitment

Kowalski, Joanne  
FY03, FY02, FY03, and FY06  
Bioinformatics of Genetic Susceptibility to Colorectal Cancer: Linking a Risk Prediction Algorithm to a Functional Genomic Database  
Faculty Recruitment

Maity, Anirban  
FY04  
Comprehensive Array-based Analysis of Somatic Mitochondrial Mutations in Smoking-related Gastrointestinal Tract Cancers

Mutanski, Genevieve M.  
FY03  
Race Disparities in Patterns of Care for Breast Cancer  
Faculty Recruitment  
Translational Research

Messersmith, Wells  
FY06  
Evaluation of Novel SRC Inhibitors in Pancreas Cancer  
Faculty Recruitment

Nelson, William and Platz, Elizabeth  
Funded: FY03  
Racial/Ethnic Variation in Steroid Hormone Concentration across Age in US Men  
Translational Research

Newhouse, Robin P.  
FY06  
Smoking Cessation Intensive Nursing Interventions (SCINI) and the Quality of Smoking Cessation Efforts in Maryland  
Translational Research

Ochs, Michael K.  
FY02  
Identification of Signaling Activity in Tumor Cells  
Faculty Recruitment

Ostermeier, Marc  
FY03  
Cancer Therapy and Diagnostics by Combinatorial DNA Insertion  
Faculty Retention

Park, Bon Ho  
FY02  
Mutational analysis of breast cancer drug sensitivity using zebrafish gene replacement technology  
FY04  
Identification of Novel Compounds that Target Tumour Resistant Breast Cancers

Paranjape, Giovanni  
FY03  
Bioinformatics for Understanding Cancer and its Causes

Plantadit, Steve  
Funded: FY04  
Patients Served by the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins  
FY04  
Clinical Trials Design  
Faculty Retention

Pili, Roberto  
FY03 and FY02  
Therapeutic applications of targeting retinoic acid receptors in prostate cancer

Platz, Elizabeth A.  
FY01  
The LIUNA Prospective Cancer Cohort Study on Cancer  
FY02  
Cigarette Smoking and Cell Cycle Control in Relation to Colorectal Adenoma  
FY04  
The Hormone Demonstration Program

Platz, Elizabeth A. and Zahora, James R.  
Funded: FY02  
Prostate Cancer Drug Development Program

Platz, Elizabeth and Chakravarti, Aravinda  
FY03, FY05, FY06, and FY07  
SKCC Cancer Prevention and Control Population Resource  
Translational Research

Platz, Elizabeth; Yegnasubramanian, Srinivasan; and Nelson, William  
FY08  
Prostate cancer: environment, methylation & inflammation

Rados, Richard B.  
FY02  
Development of a preventative and therapeutic vaccine against a broad range of human papillomavirus types

Rudin, Charles  
FY04  
A Multidisciplinary Translational Program for the Development of Treatment Strategies for Lung Cancer  
FY05  
Translational Lung Cancer Research: From Discovery to Application  
Human Oral Papillomavirus Etiology

Ruczinski, Ingo  
FY02  
Analysis of SNP microarray data using logic regression

Shah, Reetu V. and Yang, Stephen C.  
FY02  
Simian virus 40 (SV40) and human pleural malignant mesothelioma (MM)

Shapiro, Gary  
FY06  
Clinical Research in Gerontology and Oncology  
Faculty Retention

Sidransky, David  
Funded: FY05 and FY07  
Molecular Determinants of Response  
Laboratory  
Translational Research

Silberfeld, Ellen K.  
FY04  
Environmental Arsenic Exposure and Oncology  
Faculty Retention

Stillman, Francois A.  
FY04 and FY07  
Cancer Prevention in African American Young Adults  
Translational Research

Sugar, Elizabeth  
FY06  
Developing a Flexible Design for Phase I Oncology Trials with Multiple Treatments  
Faculty Retention

Tao, Xiuguan (Grant)  
FY02 and FY03  
Prostate cancer: environment, methylation & inflammation

Trimble, Cornelia L.  
FY01  
Proposal for the Development of a System Using Dimers to Identify HPV 16 E7 Specific T Cell Response  
FY02  
Center for Cervical Studies

Treck, Bruce  
FY01 and FY02  
Impact of Environmental Cadmium Exposure on Prostate Cancer Risk in the Baltimore Metropolitan Area Pilot Study  
Faculty Retention

Yoon, Yin  
FY01  
Genetic Epidemiology of Cancer

Voiculescu, Victor  
FY04  
Molecular Analysis of the Colorectal Cancer Genome

Viswanathan, Kala  
FY02 and FY03  
Association between growth factor levels, oestriol deacetylation expression and the risk of proflora-tive and noninvasive breast disease  
Faculty Recruitment  
Translational Research

Wheeland, Sarah  
FY06  
Identifying Molecular Markers for an Aggressive Basal-like Subtype of Breast Cancer  
Faculty Recruitment

Yager, James and Grooopes, John D.  
FY04 and FY07  
Plasma Proteomics Core for Cancer Prevention Research  
Translational Research

Yager, James  
FY08  
Roles of estrogen metabolism and altered gene expression in estrogen induced mammary tumorigeneis - studies using the ACI rat model
Cancer Prevention and Control Network Seminars

2004

BILLY NELSON, MD, PH.D.
The molecular basis of prostate cancer and how it informs prevention and control efforts

ELIZABETH PLATZ, SC.D., M.P.H.
A Cancer Prevention and Control Resource

JULIE BRAHMER, M.D.
Lung cancer prevention - a focus on Cox-2 inhibitors

ANN KLASSEN, PH.D.
Changing dietary behavior through education in low-resource communities

KALA VISVANATHAN, M.B.B.S.
The evaluation of broccoli sprouts tea as a chemopreventive agent for breast cancer

ANTHONY ALBERG, PH.D.
Nicotine replacement therapy use in the real world

ARAVINDA CHAKRAVARTI, PH.D.
Whole genome sequencing, a tool for cancer research

FRAN STILLMAN, ED.D.
Advancing tobacco control through community-based participatory research with young African American adults in Baltimore

ROLF HALDEN, PH.D.
Municipal sludge application in agriculture: a potential link to cancer

YIN YAO, PH.D.
Hormone demonstration project

JONATHAN SAMET, M.D.
Lung Cancer Registry, what you can and cannot do!

2006

EILEEN STEINBERGER, M.D., M.S.
Assistant Professor, Department of Epidemiology and Preventive Medicine, UMB

H. BALLANTINE CARTER, M.D.
PSA screening: Current news and views

GIOVANNI PARMIGIANI, PH.D.
Familial risk prediction: Examples from colon, pancreas and breast cancer

VICTOR VELCULESCU, M.D., PH.D.
Blueprint of breast and colorectal cancer genomes

Hugh WATERS, M.D.
Measuring the costs of environmental tobacco smoke

THOMAS LAVEIST, PH.D.
Do community factors account for race differences in smoking rates? Findings from the EDIC Study

MARTYN T. SMITH, PH.D.
Professor of Toxicology Division of Environmental Health Sciences, UC Berkeley School of Public Health

2007

MALCOLM BROCK, M.D.
Lung Cancer in HIV Patients - Is this a Different Lung Cancer?

AMY BERRINGTON, PH.D.
Co-factors in the development of ovarian cancer - results from an international collaboration

DAVID SIDRANSKY, M.D.
Molecular diagnostic studies in cancer detection and treatment

ALISON KLEIN, PH.D.
Pancreatic Cancer: Epidemiology, Genetics and Risk Assessment

SHIUBAN SUTCLIFFE, PH.D.
Infections in the etiology of prostate cancer

ALISON GEYH, PH.D.
Metal-associated ambient particulate matter exposures and lung cancer

MAXINE STITZER, PH.D.
Relapse in smoking cessation: Causes and cures

PAUL STRICKLAND, PH.D.
Use of Biomarkers to Assess Carcinogen Exposure in Etiological Studies of Cancer

JEAN FORD, M.D.
Liver, HBV, and genes

BRIAN CAFFO and DAN SHARFSTEIN
Statistical methods for Risk Determination

FREDERICK BRANCATI, M.D., M.H.S.
Diabetes and Cancer

M. CHRIS GIBBONS, M.D.
Community practice and handheld technology: From idea to implementation

JEAN FORD, M.D.
Molecular epidemiology of lung cancer
The seminars provide an opportunity for cancer researchers and clinicians to meet and interact with other cancer investigators and discuss scientific interests in translational cancer research.

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<th>2008</th>
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<th>RESEARCH MATTERS</th>
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<td><strong>Clair Snyder, Ph.D.</strong></td>
<td>Which physician specialties manage breast cancer survivors and how does that affect their care?</td>
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<td><strong>Harvey Brenner, Ph.D.</strong></td>
<td>Does economic development influence the development of cancer in industrialized nations?</td>
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<td><strong>Chris Gibbons, M.D., M.P.H.</strong></td>
<td>The emergence of Cancer Populomics</td>
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<td><strong>Gypsyamber D’Souza, Ph.D.</strong></td>
<td>Role of human papillomavirus in oropharyngeal cancer</td>
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<td><strong>Elizabeth Platz, Sc.D., M.P.H.</strong></td>
<td>Hormones and Men’s Health: Findings from the Hormone Demonstration Program</td>
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<td><strong>Rachael Stolzenberg-Solomon, Ph.D., M.P.H., R.D., Nutritional Epidemiology Branch</strong></td>
<td>Division of Cancer Epidemiology and Genetics, National Cancer Institute</td>
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<td><strong>Shyam Biswal, Ph.D.</strong></td>
<td>Decoding the environmental stress response in lung disease</td>
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<td><strong>Diane Dwyer, M.D.</strong></td>
<td>Is Maryland a high cancer incidence state? Results from the Maryland Cancer Registry</td>
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<td><strong>H. Ballentine Carter, M.D.</strong></td>
<td>Prostate Cancer: Early detection and improved survival</td>
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<td><strong>Liesha Emens, M.D., Ph.D.</strong></td>
<td>Chemotherapy-modulated vaccination for breast cancer: from bench to bedside</td>
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<td><strong>Luis Diaz, M.D.</strong></td>
<td>A simple blood test for cancer detection?</td>
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<td><strong>John Bridges, B.Ec., M.Ec., Ph.D.</strong></td>
<td>Pap smears: A consumer product</td>
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**ANNUAL CONFERENCE OF THE ACADEMIC HEALTH CENTERS**

The purpose of the conference is to:

- Highlight scientific research supported by the Maryland CRF;
- Discuss cancer screening and educational outreach initiatives;
- Identify and promote opportunities for collaboration between the Johns Hopkins Medical Institutions and the University of Maryland; and
- Identify new areas of research and public health outreach.


### CRF research leads to patented and licensed technologies and new research tools

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<td>Epigenetic Test for Colon Cancer</td>
<td>p21 Knockout of Human Mammary Epithelial Cells</td>
<td>Hand Held Patient Tracking, Education and Decision Support (TEDS) Tool</td>
<td>Nrf2 as a Target for Intervening Pulmonary and Systemic Inflammation</td>
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<td>Mutational Analysis of the Tyrosine Phosphotome in Colorectal Cancer</td>
<td>Novel Approach for Tackling Cancer Chemoresistance</td>
<td>Light Amp: Sensitive Point Mutation Detection</td>
<td>Identification of Novel Compounds that Target Tamoxifen Resistant Breast Cancers</td>
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<td>LigAmp: Sensitive Point Mutation Detection</td>
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2002

Six University of Maryland and Johns Hopkins CRF grantees augmented their research of cancer biomarkers with grants from the National Cancer Institute's Early Detection Research Network. To accelerate research of head and neck cancers, University of Maryland and Johns Hopkins investigators worked together to isolate potential biomarkers of oral cancer in tissue and saliva of oral cancer. The joint endeavor doubled the amount of patients studied. Sharing tissue samples, data, and biostatistical information expedited discovery and treatment advances.

Johns Hopkins and University of Maryland scientists collaborated on new methods for early lung cancer detection. Studies of spiral CT scans, sputum cytology, serum, biomarkers, and chemoprevention began. Microarray technology is the newest and most sophisticated method of analyzing patterns of gene expression in cancer. Artificial Neural Networks are the latest and most technologically advanced approach to analyzing clinical data. To help defray the cost of these expensive but necessary technologies, Johns Hopkins and University of Maryland investigators shared resources and worked together to identify cancer-related gene targets and interventions.

2003

The Avon Foundation joined the Kimmel Cancer Center and its community partners to further improve breast cancer care for the women of Baltimore City. The Avon Access to Breast Health Care Initiative, based on the Center's CRF community outreach model, provided additional funding for breast cancer education and screening for underserved minority and low-income women.

The Flight Attendants Medical Research Institute (FAMRI) named the Johns Hopkins Kimmel Cancer Center a Center of Excellence. FAMRI was established in 1991 with damages won in a class action suit against the tobacco industry for diseases and deaths caused to flight attendants by exposure to secondhand tobacco smoke in airline cabins. The settlement included the establishment of a not-for-profit medical research foundation with funding by the tobacco industry of $300 million. The Johns Hopkins Kimmel Cancer Center is a leading recipient of FAMRI research funding.

Investigators at Johns Hopkins, University of Maryland, and Greater Baltimore Medical Center collaborated in a study of 120 oral cancer patients to develop a diagnostic test for oral cancers using HPV as a marker. Investigators at the Kimmel Cancer Center and the University of Maryland worked together, using patients from both centers, to increase the data on pancreatic cancer. Increasing the number of patients studied will provide a better understanding of the lethal disease and help uncover new therapeutic targets.

2004

A $100,000 collaborative CRF grant for breast cancer research by the Kimmel Cancer Center's SARA SUKUMAR and University of Maryland's ANGELA BRODIE led to a $10 million Department of Defense grant to continue and expand their work.

A patient of CRF investigator CONNIE TRIMBLE read about her cervical cancer vaccine work in Kimmel Cancer Center publications and wrote her a check for $100,000 to further her research.

2005

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A patient of CRF investigator CONNIE TRIMBLE read about her cervical cancer vaccine work in Kimmel Cancer Center publications and wrote her a check for $100,000 to further her research.

2006

The community outreach infrastructure put in place through the CRF public health grant led to a $5.4 million award from the Centers for Medicare and Medicaid Services for cancer education and screening outreach to Medicare recipients.

With combined funding from the CRF, Avon Foundation, and Flight Attendant Medical Research Institute, breast cancer researcher BEN PARK, purchased chemical drug libraries to screen for compounds that specifically kill or inhibit the growth of tamoxifen-resistant breast cancer cell lines. Identifying such a drug would be a major breakthrough in treating hormonally-resistant breast cancers.

2001–2008

Collaborative Research and Leveraging Funds

“Funding research in a tightening economy is difficult. We need to increase collaboration and multiply the value of each research grant.”

John M. Colmers, M.P.H, Secretary, Maryland Department of Health and Mental Hygiene
2006 (continued)
A CRF Research Maters collaborative grant between MAUREEN BLACK of the University of Maryland and ANN KLASSEN of Johns Hopkins was used to study the impact of obesity on cancer. Experts report that 20 percent to 50 percent of fatal cancers are attributable to poor diet. Black and Klassen’s work establishes a feasible approach to reducing cancer-related dietary risk in low-income families. Data gathered from the initial CRF-sponsored study were used to obtain additional grants for intervention studies.

SHYAM BISWAL showed that sulforaphane, a compound found in broccoli sprouts, reduces inflammation of the lungs caused by cigarette smoke, allergens, and other agents, by activating a carcinogen detoxifier master gene known as Nrf2. The gene is turned on in response to environmental pollutants such as cigarette smoke, setting in motion a chain of events that protects the lungs. He used these findings to get additional funding from the National Cancer Institute and is collaborating with JULIE BRAHMER for a lung cancer prevention trial to test the effectiveness of a broccoli sprouts extract in activating the Nrf2 pathway in smokers.

HOPKINS WINS GRANT TO STUDY EPIGENOME
A team, including CRF investigators and leading epigenetic experts STEPHEN BAYLIN and JAMES HERMAN, received part of a three-year $11.7 million grant from the NIH to study the genomes of lung, brain and ovarian cancers. The Hopkins team, in a joint effort with the University of Southern California’s Nordin Comprehensive Cancer Center, will receive $780,000, and is the only group among seven institutions selected by the NIH to study each cancer’s “epigenetic” profile. Epigenetic changes modify the DNA without mutating the chemical base pairs that together form the letters of genetic code. Baylin, Herman, and colleagues will look for tiny methyl groups that inappropriately attach to the “on” switch of genes and block their expression.

2007
The Maryland Stem Cell Research Commission funded 24 projects under the Maryland Stem Cell Research Act of 2006. CRF investigators SHYAM BISWAL was among the seven Investigator-Initiated Grant recipients from Johns Hopkins.

A Johns Hopkins and University of Maryland research team developed a patient navigation electronic log (PANEL), a computerized system providing them with strategies to determine patient needs and improve coordination of prostate cancer screening, and reduce barriers to care.

The Johns Hopkins Bloomberg School of Public Health is awarded the Science to Achieve Results (STAR) grant from the Environmental Protection Agency to form the Johns Hopkins Participate Matter Research Group. Combining this grant with CRF funding allowed investigators to study the health risks of particulate matter (a mixture of solid particles and liquid droplets in the air, including everything from smoke and fumes to dust and pollen) air pollution. A 2002 study of 500,000 adults found an 8 percent increase in lung cancer risk due to increased levels of fine particulate matter in the air.

CRF investigator ALLISON KLEIN takes advantage of the Johns Hopkins-based National Familial Pancreatic Tumor Registry, the world’s largest database on familial pancreatic cancer, to better understand the risk factors for pancreatic cancer. The goal is to improve survival through early detection by identifying genetic markers of risk that could be the target of new screening tests for this lethal form of cancer.

The Kimmel Cancer Center hosted Investing in Cancer Research: Crossing the Translational Divide, a biotechnology conference to educate potential investors about cancer center research and technologies. The Johns Hopkins Medical Institutions 2-million-square-foot Science + Technology Park, currently under construction, was announced. Howard Hughes Medical Institute, Cangen Biotechnologies, and Biomarker Strategies are among those purchasing space in the park.

TO STUDY EPIDEMGENE
A Johns Hopkins and University of Maryland, in screening 1280 compounds that can knock down a cancer gene known as Nrf2. The best candidate will be studied in lung cancer patients in an block resistance to chemotherapy.

2008
A research team, including CRF investigator VICTOR VELCULESCU used early findings in colon cancer genetics to attract a consortium of funders, including in addition to the CRF, The Virginia and D.K. Ludwig Fund for Cancer Research, the Sol Goldman Charitable Trust and Lillian Goldman Charitable Trust, the Ludwig Foundation, the Department of Defense, Pew Charitable Trusts, The Palmetto Health Foundation, the State of Ohio Biomedical Research and Technology Transfer Commission, the Clayton Fund, the Blaustein Foundation, the National Colorectal Cancer Research Alliance, the Susan G. Koman Foundation, the Aven Foundation, the Flight Attendant Medical Research Institute, the V Foundation for Cancer Research, the Summer Running Fund, Pew Charitable Trusts, Pediatric Brain Tumor Foundation Institute, Henschelchon Foundation, Alex’s Lemonade Stand Foundation, American Brain Tumor Association, American Society of Clinical Oncology, Brain Tumor Research Fund, Michael Rolfe Pancreatic Cancer Foundation, Joseph C. Monastria Foundation, the family and friends of George Rubis, Broad Foundation, and the Emerald Foundation.

Their multi-million dollar research resulted in the genetic blueprints for breast, colon, brain, and pancreatic cancers.

The Alliance, a group of high-level business executives that aids faculty in commercializing their inventions, has awarded ANIRBAN MAITRA, $50,000 for his drug delivery system that makes cancer therapies easier to give to patients.

SHYAM BISWAL from Johns Hopkins is collaborating with GEOFFREY GUMIN from University of Maryland, in screening 1280 compounds that can knock down a cancer gene known as Nrf2. The best candidate will be studied in lung cancer patients in an block resistance to chemotherapy.
DID YOU KNOW...

Maryland went from leading the nation in cancer deaths in the 80s to 19th today. Virtually everywhere throughout the state—in Baltimore City, Prince Georges County, Montgomery County, Baltimore County, Anne Arundel County—cancer death rates went down among Blacks, Whites, men and women.

From 1996-2000, Maryland had the third highest colorectal cancer death rates in the nation. Today we rank 13th. Cancer death rate disparities between Black and Whites—a major focus of CRF research and community outreach—declined by 50 percent between 2000 and 2005. Furthermore, our disparity rates are declining more rapidly than the national average.

Disparity rates for cancer have seen significantly greater improvements than rates for other diseases, including heart disease.

Between 2000 and 2004, prostate cancer death rates among African-American men, the focus of the CRF community outreach at Johns Hopkins, declined by over 16 percent. Disparities in the death rates of Black and White men narrowed by nearly 20 percent.

Using results from CRF supported research, investigators have leveraged an additional $300 million in grants.

Sources: The Centers for Disease Control and the Maryland Vital Statistics Administration.