TRANSFORMING PROSTATE CANCER
DETECTION, DIAGNOSIS, AND TREATMENT
PROMISE & PROGRESS
2012/2013 VOLUME ONE

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CANCER NEWS REVIEW, MONTHLY PODCAST FROM DIRECTOR WILLIAM NELSON

MEDIA CENTER, VIDEO AND PODCAST GALLERY

Promise & Progress WEB EXCLUSIVES

SEARCH FOR JOHNS HOPKINS MEDICINE

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On the Cover: Former Temptations singer Damon Harris, at his Owings Mills home.

For additional copies of this publication or further information about the Kimmel Cancer Center, please call (410) 955-1287 or email mehlva@jhm.edu
THE KIMMEL CANCER Center is an incredible cancer discovery engine. Our laboratory scientists have made world-class findings that have revolutionized cancer research. Still, what we are most proud of is how we are using these breakthroughs to improve the experience and outcomes of patients. This only occurs when scientists work side by side with clinicians, and this is the Kimmel Cancer Center model. A new clinical arm of our genetic and epigenetic sequencing laboratories (see page 40) is focused on translating these revolutionary discoveries about the unique molecular blueprints of cancers into clinical tests that will help identify those people most at risk and guide diagnosis and treatment.

WE ARE NOT CONTENT WITH THE STATUS QUO. WITH DISCOVERY COMES THE OPPORTUNITY, AND I BELIEVE THE OBLIGATION, TO RE-EVALUATE AND IMPROVE HOW WE DELIVER CANCER CARE.

We are not content with the status quo. With discovery comes the opportunity, and I believe the obligation, to re-evaluate and improve how we deliver cancer care. In this issue, you will read about significant advances in how we detect, diagnose and treat prostate cancer. We recognized that this is a disease that is too frequently overdetected and overtreated but, at the same time, is a leading killer of men. With the multidisciplinary expertise of some of the world’s best urologists, oncologists, radiation oncologists, pathologists, radiologists, and cancer scientists we are transforming how prostate cancer screening and treatment is delivered with evidence-based, personalized care that gets interventions to patients who we know will benefit and moves them away from those we know will only be harmed. At the same time, we are using the clinical characteristics that distinguish one group from the other to develop novel prevention approaches, better screening and diagnostic markers, and more effective treatments.

As a prostate cancer clinician-scientist, and a member of this team, I am so proud of this work. As the Kimmel Cancer Center Director, I am excited about the possibilities because I recognize that much of what we learned about prostate cancer can be applied to make similar advances against other cancer types.

Our ability to make these unprecedented gains is tied directly to the generosity of our donors. The National Cancer Institute, the Department of Defense, Sidney Kimmel, David H. Koch, the Commonwealth Foundation for Cancer Research, the Prostate Cancer Foundation, Safeway, Jones Day, AEGON, the Patrick C. Walsh Prostate Cancer Research Fund, the Maryland Cigarette Restitution Fund, and many dedicated individual donors are among the contributors who have made the Johns Hopkins prostate cancer program one of the strongest and most productive in the world.

Johns Hopkins clinicians and scientists have a long history of pioneering advances against prostate cancer. It was here that the first radical prostatectomy was performed, and here that it was reinvented. Here, laboratory scientists developed the first animal models to characterize the properties and types of prostate cancer, and here, current researchers and clinicians build upon this work to deliver 21st century personalized cancer medicine. This bench-to-bedside tradition is what sets Johns Hopkins apart and ensures continued progress against prostate cancer and all cancers.

William G. Nelson, M.D., Ph.D.
Marion I. Knott Professor and Director
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
HALF-MATCHED TRANSPLANTS MAY CURE SICKLE CELL DISEASE

Blood, September 6, 2012

Kimmel Cancer Center bone marrow transplant researcher Javier Bolanos-Meade, M.D., and team have shown that half-matched (haplo-identical) bone marrow transplants can cure sickle cell anemia, a painful and debilitating blood-forming disease in which red blood cells are shaped like crescents instead of discs and clog blood vessels, cutting off oxygen to tissues and organs.

Bone marrow transplant replaces the diseased marrow with the healthy marrow of a donor. After an average of two years of follow-up, eight of 14 patients treated with a half-identical transplant and another three who all received a fully matched bone marrow transplant remain symptom free. Ten patients are believed to be cured of their sickle cell disease.

 Patients with severe sickle cell disease (SCD) face shortened life spans, intractable pain and eventual organ damage as a result of their disease. SCD primarily affects African Americans. Most patients die before age 50, and many suffer poor quality of life with frequent episodes of "off-the-charts" pain, and an increased risk for kidney failure, stroke, deep-vein thrombosis, and lung disease. The ability to safely use half-matching donors (parents, most siblings, and all children of the patient) makes bone marrow transplant an effective option for the majority of sickle cell patients. Kimmel Cancer investigators Ephraim Fuchs, M.D., and Leo Luznik, M.D., pioneered the haploidentical version of the therapy to help patients who do not have matching donors.

“We’re trying to reformat the blood system and give patients new blood cells to replace the diseased ones, much like you would replace a computer’s circuitry with an entirely new hard drive,” says Robert Brodsky, M.D., Director of Hematology and The Johns Hopkins Family Professor of Medicine and Oncology. “While bone marrow transplants have long been known to cure sickle cell disease, only a small percentage of patients have fully matched, eligible donors.”

Six of the transplants were not successful. The patients own diseased blood cells eventually returned. Work to improve the rate of bone marrow engraftment in half-identical transplants for sickle cell is ongoing.

Funding for the research was provided by the National Cancer Institute and National Institutes of Health grants P01CA15396 and K23HL083089 and Sistema Nacional de Investigadores (Mexico). ●

EMBRYO GENE LINKED TO LETHAL LUNG CANCER

Nature Genetics, September 2, 2012

Scientists from several institutions, led by researchers at the Kimmel Cancer Center, completed a comprehensive map of the genetic mutations linked to a lethal type of lung cancer, known as small cell lung cancer (SCLC). “Small cell lung cancers are very aggressive. Most are found late, when the cancer has spread, and typically survival is less than a year after diagnosis,” says Charles Rudin, M.D., Ph.D., professor of oncology and Director of the Kimmel Cancer Center Lung Cancer Therapeutics Program. “Our genomic studies may help identify genetic pathways responsible for the disease and give us new ideas on developing drugs to treat it.”

Among the genetic alterations identified by the investigators was an increase in the number of copies (amplification) of a gene called SOX2. Normal cells should contain just two copies of the gene (one copy from each parent), which is involved in embryo development. In cancer, researchers suspect that amplification causes an overproduction of SOX2 proteins that, in turn, reignites and sustains cell growth associated with tumor formation. “SOX2 is an important clue in finding new ways to treat small cell lung cancer,” says Rudin. “We may be able to link a patient’s outcome to this gene and develop a drug to target it or other genes it regulates.”

The research was funded by the Burroughs Wellcome Fund, the Flight Attendant Medical Research Institute, the National Cancer Institute grants P50CA058184, P50CA70907, and P50CA058187, the CAPES Foundation, and the Ministry of Education of Brazil. ●
**UPDATE: NOVEL TECHNIQUE REVERTS CELL TO EMBRYONIC STATE**

Public Library of Science, August 8, 2012

The same scientist who last year transformed human blood cells into beating heart cells has now developed a safe and super efficient method to turn the clock back on blood cells, reverting them to the primitive state from which they derived. This form, known as the stem cell state, is the point at which blood cells may develop into any other type of cell in the body.

The work by Elias Zambidis, M.D., Ph.D., assistant professor of oncology and pediatrics at the Institute for Cell Engineering and the Kimmel Cancer Center is the latest work in his ongoing effort to efficiently and consistently convert adult blood cells into stem cells that can be used for clinical research in place of human embryonic stem cells.

“Taking a cell from an adult and converting it all the way back to the way it was when that person was a 6-day-old embryo creates a completely new biology toward our understanding of how cells age and what happens when things go wrong, as in cancer development,” Zambidis says.

More common methods use viruses to convert cells to a stem cell state, and among hundreds of blood cells, they typically obtain a successful conversion in one to two cells. Zambidis chose not to use viruses because they can mutate genes and initiate cancers—the very disease he is working to fight—in newly transformed cells. Instead, he and his team opted to use plasmids, rings of DNA that replicate briefly inside cells and then degrade, and umbilical cord blood treated with growth factors to transform cells to the primitive stem cell state. This technique resulted in a successful conversion of 50 to 60 percent of cells.

The work was supported by the National Institutes of Health National Heart, Lung, and Blood Institute, grants 1U01HL099775 and U01HL100397, the National Cancer Institute grant CA60441, and the Maryland Stem Cell Research Fund grants2011-MSCRF II-0008-00 and 2007-MSCRF II-0379-00.

**DETECTABLE LESIONS WARN OF HEREDITARY PANCREAS CANCER**

Gastroenterology, April 2012

A Johns Hopkins-led study of 216 adults at high risk for hereditary pancreas cancer found that more than four in 10 people have small lesions in their pancreas long before they have any symptoms of the deadly disease. The prevalence of the lesions increases with age, and are most common in people age 50 and older. Ultrasound done by endoscopy was better than MRI and significantly better than CT scans at finding these potential precursors to pancreas cancer.

About 10 to 15 percent of all pancreas cancers are hereditary. This research, led by Marcia Irene Canto, M.D., M.H.S., professor of gastroenterology and oncology, could help reduce the death rate from hereditary pancreas cancer, which is generally fatal once these lesions begin to grow and symptoms appear. “We now know that although these high-risk patients often tend to develop pancreatic lesions, we can detect the lesions, track them over time and remove them before they become cancer,” says Canto.

Not all pancreatic cysts become pancreas cancer. Earlier research by Bert Vogelstein, M.D., and his team in the Ludwig Center for Cancer Genetics, are developing biomarkers that predict the malignant potential of cysts. Researchers hope those findings used in conjunction with the results from this new study will help experts find and treat potentially lethal pancreas cancers while they are still curable.

The research was supported by the National Cancer Institute Specialized Programs of Research Excellence (SPORE), The Lustgarten Foundation for Pancreatic Cancer Research, The Michael Rolfe Foundation, Olympus Corporation, Cooke Medical, the Karp Family, H.H. & M. Metals Inc. Fund for Cancer Research and ChiRhoClin, Inc.

**DRUG TREATMENT REPROGRAMS CANCER CELLS**

Cancer Cell, March 20, 2012

Experimenting with cells in culture, researchers obtained promising results with two drugs once considered too toxic for human cancer treatment. The drugs, azacitidine (AZA) and decitabine (DAC), are epigenetic-targeted drugs and work to correct cancer-causing biochemical alterations to the environment of DNA.

The researchers said the drugs also were found to take aim at a small but dangerous subpopulation of self-renewing cells, sometimes referred to as cancer stem cells, which evade most cancer drugs and cause recurrence and spread. The study produced evidence that low doses of the drugs could cause antitumor responses in breast, lung, and colon cancers.

Conventional chemotherapy agents work by indiscriminately poisoning and killing rapidly dividing cells, including cancer cells, by damaging cellular machinery and DNA. “In contrast, low doses of AZA and DAC may re-activate genes that stop cancer growth without causing immediate cell-killing or DNA damage,” says Stephen Baylin, M.D., Ludwig Professor of Oncology and Deputy Director of the Kimmel Cancer Center.

Baylin and his colleague Cynthia Zahnow, Ph.D., assistant professor of oncology and the Evelyn Grolman Glick Scholar, decided to take another look at the drugs after they had showed benefit at low doses in patients with a pre-leukemic disorder called myelodysplastic syndrome (MDS). Their new work revealed that the low-dose therapy reversed cancer cell gene pathways, including those controlling cell cycle, cell repair, cell maturation, cell differentiation, immune cell interaction, and cell death. Effects varied among individual tumor cells, but the scientists generally saw that cancer cells reverted to a more normal state and eventually died.

The results of clinical trials in lung cancer, led by Charles Rudin, M.D., Ph.D., professor of oncology and Director

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of the Lung Cancer Therapeutics Program, and published in 2011 in Cancer Discovery, also indicate that the drugs make tumors more responsive to standard anticancer drug treatment. This means, they say, that the drugs could become part of a combined treatment approach rather than a stand-alone therapy and as part of personalized approaches in patients whose cancers fit specific epigenetic and genetic profiles.

The research was funded by a SPORE grant for lung cancer from the National Institutes of Health, the Hudson Trust Foundation, Entertainment Industry Foundation, Lee Jeans, Samuel Waxman Cancer Research Foundation, Department of Defense Breast Cancer Research Program, Huntsman Cancer Foundation, and the Cindy Rosencrans Fund for Triple Negative Breast Cancer Research. All of the studies have been accelerated by funding from the Stand Up To Cancer (SU2C) project in partnership with the American Association of Cancer Research (AACR).

BRAIN CANCER EXPERTS SET THE RECORD STRAIGHT
Oncotarget, January 2012
Laboratory findings from Kimmel Cancer Center brain cancer researchers refute outside studies that suggest blood vessels that form within brain cancers are largely made up of cancer cells. “We don’t question whether brain cancer cells have the potential to express blood vessel markers and may occasionally find their way into blood vessels, but we do question the extent to which this happens,” says Charles Eberhart, M.D., Ph.D., chief of neuropathology and professor of pathology, ophthalmology, and oncology. “In general, we find no evidence in our study that these vessels contain substantial amounts of cancer cells.”

Eberhart became aware of claims about the tumorous nature of tumor blood vessels when students solicited his opinion on journal articles on the topic. “My first reaction to this research was ‘How could this be true?’” says Eberhart. “Our clinical experience examining tissue from brain cancers does not support it.” Research has long demonstrated that malignant brain tumors contain large numbers of blood vessels to feed their growing demand for nutrients. The blood vessels are formed when tumors pump out growth factors that increase vessel production. Such studies opened the door to treatment strategies that specifically targeted blood-vessel growth and the vessel cells themselves. More recently, scientists in Italy and at the Memorial Sloan Kettering Cancer Center in New York published results of studies suggesting that these tumor blood vessels are made by primitive types of brain cancer cells and were more prone to drug resistance.

Eberhart teamed up with colleagues at the Dana Farber Cancer Institute and Harvard Medical School to examine the molecular features of brain cancer cells from 100 patients and used biomarkers as well as known brain-cancer related gene mutations to distinguish normal vascular cells from cancer cells. They found that only 10 percent of the samples contained vascular cells that had cancer gene mutations, and in those rare tumor samples, only a few cells were affected.

These findings, that refute the prevalence of cancer-like blood vessels, call into question the use and value of anticancer drugs that target blood vessels in brain cancer patients.

Funding for the study was provided by the National Institutes of Health grants T32CA067751 and 5R01NS055089.

NEW FINDINGS ON BRCA1 BREAST CANCER GENE
Kimmel Cancer Center breast cancer researchers have shown that the inactivation of a single copy of the breast cancer gene BRCA1 leaves breast cells vulnerable to cancer by reducing their ability to repair DNA damage, causing genetic instability, the hallmark of cancer. An inherited mutation in BRCA1 is the leading risk factor for hereditary breast cancer, prompting preventive mastectomies or close monitoring. Learn how these new findings may aid development of drugs to prevent hereditary breast cancer and tools to identify women who benefit most from prophylactic treatments.

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SEQUENCING OUR GENES: IS CANCER WRITTEN IN OUR DNA?
Technology called next generation sequencing can be used to reveal an individual’s complete and entire DNA (whole genome). Right now, it costs about $5000 to sequence an individual’s whole genome, but the price tag is decreasing rapidly. With its increasing affordability, many have suggested that it could be used to identify individuals who were likely to develop cancer in the future as well as those who would be safe from the disease. But, will it?

PROVOKING AN IMMUNE RESPONSE TO CANCER
Breakthrough discoveries have revealed an immune inhibitory checkpoint called PD-1 that is co-opted by tumors to shut down an immune response to cancer cells. Two clinical trials that used antibodies to block PD-1 and a related resulted in significant and long lasting responses against melanoma skin cancer, renal cell (kidney) cancer, and lung cancer. Read the story on page 40.

PREDICTING WHICH LUNG CANCER DRUGS WILL WORK
Researchers showed that DNA changes in a gene that drives the growth of one type of lung cancer could make cancers cells resistant to treatment. The findings indicate which classes of drugs won’t work and which ones may be the most effective. Learn more.

THE LIFE CLINIC
The Life Clinic at the Johns Hopkins Kimmel Cancer Center assesses and monitors cancer survivors to help manage long term complications from previous cancer treatments.

WWW.HOPSKINSKIMMELCANCERCENTER.ORG
When does the new Bayview clinic open and what can patients expect? My plan is to take the Kimmel Cancer Center’s Bayview program from a community hospital to a fully participating academic arm of Johns Hopkins. We expect the clinical areas to open in the Spring of 2013. They will include a medical oncology treatment area overlooking a beautiful garden with 22 infusion chairs and private exam rooms, and a radiation oncology treatment area with two linear accelerators. We will have a multidisciplinary lung cancer clinic to bring together for patients, in one clinic, all of the specialties involved in the diagnosis and treatment of lung cancer. What makes our clinic particularly unique is its focus on cancer prevention in addition to cancer treatment.

What is your strategy for cancer prevention? The Kimmel Cancer Center Bayview campus will have a dedicated center for cancer prevention to balance the need to take care of patients with established cancers with an effort to identify and help people at risk. There are tens of millions of Americans who are at permanent increased risk of developing lung cancer because of a prior or current history of smoking. Screening for early lung cancer using low-dose spiral CT scans save lives, and we plan to provide this screening for people with a history of smoking, but we are also taking it a step further and planning interventions for people with premalignant nodules.

Nodules (small abnormal spots on the lung) are identified in about 30 percent of heavy smokers who have spiral CT scans. Lung nodules are quite common, particularly in smokers, but they are not always cancer. We have developed a nodule clinic in collaboration with the Pulmonology Department to monitor and manage people with nodules discovered through spiral CT. We will develop protocols and test prevention strategies that we hope will keep nodules from progressing to lung cancer. The Kimmel Cancer Center Bayview team will be among the very first in the world to use screening as a research tool. With our Center’s depth of expertise in the genetic and epigenetic causes of cancer, we can make inroads in prevention that are not being done anywhere else. We will take an at-risk population and personalize lung cancer risk assessment and prevention. People with precancerous lesions will have the opportunity to participate in intervention trials that target molecular and cellular changes that this research shows can lead to lung cancer in future years with the aim of reversing the process.

Does this work increase our understanding of lung cancer? Smoking is the leading cause of lung cancer. By bringing these people in to the Hopkins system, we will be able to better understand tobacco exposure and lung cancer risk, genetic features, and family history. We can begin to make progress by studying and evaluating treatments that target the very earliest, premalignant changes that lead to lung cancer—take out a cancer before it actually is a cancer. I think we have the opportunity to make unprecedented strides against lung cancer.
[COVER STORY]
Transforming Prostate Cancer

DETECTION, DIAGNOSIS AND TREATMENT

by Valerie Matthews Mehl
PROSTATE CANCER IS AN ICONOCLAST AMONG CANCERS. It is at odds with what experts know to be the optimal approach for most cancers: Find it early and treat it early. Prostate cancer is different. It may be one of the few cancers humans can live with. It is most often slow growing, and even late-stage cancers can many times be held in check for years. On the other hand, it is a cancer that kills many men. It is the second leading cause of cancer death for men. The challenge, then, is deciphering the “good” prostate cancer from the “bad.” As a result, it is a model for personalized cancer medicine as Johns Hopkins urologists and cancer scientists and clinicians lead the way, using the most advanced science and technology to redefine for the world who to screen, who to treat, and who to safely leave alone.

WHERE WE CAME FROM, WHERE WE ARE GOING
The innovation that sets the Johns Hopkins prostate cancer program apart can be traced, in part, to the inventive thinking of Patrick Walsh and Donald Coffey. They set the standard—challenging clinicians and investigators to think beyond the status quo; beyond what is adequate to what is extraordinary. Walsh developed an anatomical, nerve-sparing approach to surgery that, for the first time, cut out and cured prostate cancer without causing devastating side effects for men. Patients the world over traveled to Johns Hopkins to have Walsh’s surgery, and urologists-in-training sought to come to Johns Hopkins to learn the pioneering technique. Today, it remains the most common surgery performed at Johns Hopkins.

Forward thinking, Walsh compiled an extensive database of thousands of patients and followed them for 30 years. What he and others learned from these men became the laboratory fodder for the bespectacled inquisitor Donald Coffey who began exploring the basic biology of prostate cancer and provided some of the first insights to the subtle and unique variations of cancer DNA. Like Walsh, he shared what he learned. One of Johns Hopkins School of Medicine’s first triple professors, Coffee is the consummate teacher, inspiring generations of researchers to not only look for answers but to ask questions that had never before been asked.

Those who studied under Walsh and Coffey became leaders in prostate cancer treatment and research at Johns Hopkins and around the world. Walsh, a clinician, and Coffey, a basic scientist, embodied the bench-to-bedside collaborations that are the hallmark of Johns Hopkins medicine and provided strong roots for a prostate cancer program.

This is, in many ways, the golden age. Generations of clinicians and investigators provide incredible depth to the prostate cancer program much like grandparents do for a family. Today, under the leadership of Kimmel Cancer Center Director William Nelson, Brady Urological Institute Director Alan Partin, and Radiation Oncology and Molecular Radiation Sciences Director Theodore DeWeese, Johns Hopkins experts, from a wide range of disciplines, are on the forefront poised to transform how prostate cancer is detected, diagnosed, and treated.
Donald Coffey trainees have gone on to become titans in cancer discovery. Among them is Kimmel Cancer Center Director William Nelson, Brady Urological Institute Director Alan Partin, renowned cancer genetics pioneer Bert Vogelstein, and Prostate Cancer Foundation President Jonathan Simons.

**FIRST DO NO HARM**
The purpose of early detection is to catch a cancer early so that it can be removed or destroyed before it causes harm. It makes sense for most cancers. The problem with detecting prostate cancer early, however, is that the diagnostic procedures and treatments can sometimes, particularly in older men, cause more harm than the disease itself.

PSA (Prostate Specific Antigen), the test that makes the early detection of prostate cancer possible, is at the center of the dilemma. Recently, the United States Preventive Task Force recommended against routine PSA testing for early detection claiming the harms outweighed the benefits. Their announcement gained widespread attention, but the truth is, experts at Johns Hopkins had been evaluating the test and changing prostate cancer screening and treatment long before the U.S. Preventive Task Force weighed in.

“We’ve known for a long time that there is a lot of harm that can potentially come with PSA testing,” says, urologist H. Ballentine Carter who has studied and evaluated the test in large populations of men for more than 20 years. Carter and other Johns Hopkins prostate cancer experts say that PSA is not inherently a bad test as it has been characterized in recent headlines. The problem, they say, is not so much with the PSA test, but instead how the test is used.

Before the Prostate Specific Antigen test, or PSA as it is now commonly known, hit the market in the late 1980s, prostate cancer was essentially an untreatable disease. There was no method for finding the cancer, and men went to the doctor only after they began experiencing symptoms, such as trouble urinating or blood in their urine. By that time, the cancer was already well advanced, and it could not be cured. Surgery was used primarily to relieve symptoms, such as bladder obstructions caused by tumors, and it often left men incontinent and impotent. For a man with prostate cancer, it seemed that if the cancer did not claim his life, it certainly would claim his quality of life.

It is no surprise, then, that when a test was developed that could detect the cancer early, before there were any symptoms, it was going to be used. Imagine, Carter says, if such a test existed for pancreas or lung cancer. Overdetection or not, people would be standing in line to get the test.

With no science to guide when prostate cancer screening should begin and how often it should be done, however, the nation, overzealously embarked on a practice of overscreening, overdetecting, and overtreating the cancer with free screenings and “awareness” campaigns that helped fuel the trend.

The result was a dramatic increase in prostate cancer incidence, and most experts agreed that many of the cancers detected would have never caused any harm. Doctors were finding a lot of prostate cancers, but many of them, Johns Hopkins scientists found, would never be a problem. “Now,” Carter says, “we must move to a more measured approach.”

He and other Johns Hopkins prostate cancer experts have put medical science back in the equation and using sound research to determine how best to screen for prostate cancer and how to tease out the prostate cancers that are likely to kill from those less aggressive forms that may not require treatment.

**PERSONALIZED CANCER SCREENING**
The numbers are staggering. Each year 20 million men get screened with PSA. Many of them undergo unnecessary biopsies, suffer complications such as infection and bleeding, and still others have surgery, radiation treatment, hormonal therapies, and drug treatments that have unpleasant side effects. Out of all of these men, less than one-third of 1 percent will die from the disease. “It's clear that for many men, the benefits may be small and the harms significant,” says health policy expert and Maryland Cigarette Restitution Fund supported investigator Craig Pollack. The challenge is figuring out from among the masses, which men will benefit from screening and which ones will not.

Confusion abounds, says Pollack. Ask patients why they get screened, and they say it is because their doctor recommended it. Ask doctors why they recommend screening, and they say their patients expect it. While Pollack finds that most primary care providers he has surveyed recognize the issues surrounding routine PSA screening, they are unsure about how to explain it to their patients.

“There are clearly some misperceptions,” Pollack says, “and since the majority of screening occurs in the community, we need to provide them with a decision-
making tool that can help them improve their practice.”

Such a tool, a novel computer-based system, which can be integrated with patients’ electronic medical records, was developed by Carter, Pollack, cancer prevention and control expert Elizabeth Platz, and other Johns Hopkins cancer and public health experts. It will be piloted in Johns Hopkins Community Physicians offices throughout Maryland. They hope it will help primary care providers discuss prostate cancer screening with their patients and direct PSA to men who will benefit and away from those who will not.

The decision-making tool takes into account age and personal medical history, along with previous PSA test results and serves as an interactive guide for physicians to use when talking to patients about prostate cancer screening. Pollack and his colleagues found that while most physicians said they took age and life expectancy into account when deciding to order PSA screening, many also said they had a hard time estimating life expectancy in their patients and welcomed help in this area.

Screening is not one size fits all, says Carter. While Pollack acknowledges that making the shift from a population approach, in which everyone is screened, to an individualized approach, directed to only those who good research tells us will benefit, can be challenging. Men who are not recommended for screening, particularly if they have been screened in the past, may be concerned, and doctors may worry they could miss a cancer. However, Pollack says there is conclusive evidence that annual screening is not necessary for everyone. “An individualized approach to an individualized approach, in which everyone is screened, ultimately treatm ent, in people we know, will benefit and increase it among people who will,” Carter says. Men have grown to expect PSA screening to be part of their annual physical. This tool helps address misperceptions about screening and facilitates discussions that will help doctors and patients make more informed decisions. Carter has conducted large population studies involving thousands of men, and the data overwhelmingly show that men over age 75 are more likely to die with prostate cancer than of it, particularly if they have other more pressing health problems. As a result, these men will not benefit from PSA, and Carter says doctors should explain that to them. Kimmel Cancer Center director and prostate cancer expert William Nelson frames it this way, “I tell men who are over 75 and considering routine screening, ‘You don’t need it. You’ve won. Prostate cancer is not going to be a problem for you.’”

If the doctor and patient determine screening would be beneficial, the tool also provides recommendations for when and how often to rescreen.

With all of the confusion, clinician
Michael Carducci wants to be sure that men who have prostate cancer understand that the PSA controversy only involves screening. PSA, he says, remains a vital tool in monitoring men who have already been diagnosed and in determining if there is a medical problem in men who are experiencing symptoms. “If you are a guy who is up five times a night going to the bathroom, you have blood in your urine, or erectile dysfunction. This is no longer screening. This is diagnosis,” says Carducci. “It is important that men understand the difference.”

**TO TREAT OR NOT TO TREAT**

Some of the greatest potential of personalized medicine is in using our new knowledge about the biology of cancer to get the right treatments to the right patients. Sometimes the right treatment may be no treatment.

One important way to reduce harm to men is to individualize the management of prostate cancer. PSA alone is not responsible for the adverse affects men have suffered; it has been what doctors have done with PSA — mainly overtreating the disease. When a man is diagnosed with cancer, Carter says, it is important for him to know that invasive treatments are not the only option.

Treatments for prostate cancer can include the surgical removal of the prostate, radiation, hormonal therapies, and chemotherapy. Each of these has the potential to cause serious problems, such as erectile dysfunction, impotence, and urinary incontinence or bowel damage. For many men, treatment is clearly the best option, and our prostate cancer clinicians are among the best in the world.

Johns Hopkins clinicians have pioneered surgical, radiation, and drug remedies for the disease, but they have also been on the forefront of a nontreatment approach. It is called active surveillance — active being the key word.

Carter, although one of the world’s leading prostate cancer surgeons, believes that putting the scalpel aside is sometimes the best tactic for men who are diagnosed with a low-grade form of the disease. The approach has been the focus of research in the Brady Urological Institute at Johns Hopkins since 1995. Data gleaned from several large studies unequivocally showed that many men with low-grade disease would never be harmed by their cancer but could be, and all too often are, harmed by treatment. “The majority of men diagnosed with prostate cancer each year are over 65 and have a low risk of dying of their disease if treatment is deferred,” says Carter. “Yet, more than 90 percent of these men, including 80 percent who are over age 75, are likely to choose some form of treatment. Active surveillance addresses excessive treat-

**“I TELL MEN WHO ARE OVER 75 AND CONSIDERING ROUTINE SCREENING, ‘YOU DON’T NEED IT. YOU’VE WON. PROSTATE CANCER IS NOT GOING TO BE A PROBLEM FOR YOU.’”**

ment of milder stages of prostate cancer, especially in seniors.”

About 40 percent of men are diagnosed with low-risk disease, and for a significant number of them, active surveillance offers a way to very carefully monitor their cancer and give them the option to delay treatment as long as it does not progress. Many of these men will never require treatment, but if they do, careful surveillance allows the growing cancer to be spotted and treated while it is still curable. A National Cancer Institute (NCI) model that uses computer simulation to determine patient outcomes evaluated all of Carter’s active surveillance data and compared it to data from men who would have qualified for active surveillance but chose surgery. In a worst-case scenario, the NCI model found that over a 15-year period, men who chose active surveillance stood to gain an average of seven additional years of not being treated, and at the most, risked losing three months of life.

Pennsylvania businessman Alex Cameron was one of the first participants in active surveillance. Cameron was in his late 50s in 1999 when he was diagnosed with prostate cancer and began exploring options including hormone therapy, brachytherapy, and surgery. In his research, he also learned of Carter’s active surveillance approach and scheduled an appointment. He admits that with a wife, three daughters, and eight grandchildren to live for, the idea of leaving the cancer alone was somewhat troubling to him and his loved ones. Cameron’s prostate cancer fit the parameters for active surveillance. He had a low Gleason score and his cancer was very slow growing. “Active surveillance sounded like a win-win good thing,” says Cameron. He says regular biopsies done under local anesthesia to monitor his cancer were a minor inconvenience in exchange for his ongoing and treatment-free health. He says he was also comforted by the knowledge that five of the world’s best prostate cancer pathologists were reviewing his biopsy samples. Today, at age 71, Cameron remains active and healthy and confident that he made the right decision.

“For any guy in my situation,” he says, “active surveillance is the way to go.”

Cameron is among the more than 1,000 men who have participated in active surveillance since Johns Hopkins began offering it 16 years ago, and there are currently about 600 men enrolled. The average participant is 67 or older. This option, Carter says, is for men who are likely to live out their natural lives without being harmed by prostate cancer. In other words, prostate cancer is not going to kill them. The men have a PSA test and rectal exam every six months as well as an annual biopsy to carefully monitor their cancer. More recently, Carter has added MRI (magnetic resonance imaging) to surveillance. “We know that there is potential to underestimate the extent of disease in some men, and MRI helps us make sure we haven’t missed anything,” says Carter. “A recent study showed that when MRI found there was no cancer there, there was really no cancer there.”

For many years, Johns Hopkins was the only cancer center to offer active surveillance. This is, in part, because medical reimbursement is a fee-for-service system that favors procedures. Johns Hopkins urologists, arguably the best
trained in the world, were the only ones willing to explore the possibility of a better option for some patients.

Endorsement of active surveillance by the Prostate Cancer Foundation and heightened concerns about overtreatment stemming from the U.S. Preventive Task Force’s recommendation, is now bringing this “no-treatment” treatment new consideration.

The Prostate Cancer Foundation is working to provide patients more assurance and has established the National Proactive Surveillance Network, a Web-based system (NPSN.net) that provides education about active surveillance and helps patients find participating doctors. Soon, patients and physicians will be able to securely access the system to enter, review, and track their own data. Men participating in active surveillance would be able to enter all of their PSA data and track their personal results to see where they fall in respect to other participants.

MOLECULAR REASSURANCE
Still, many men, upon learning they have prostate cancer, are uncomfortable leaving the cancer untreated. “They need stronger, quantifiable reassurance that their cancer won’t hurt them, and we don’t have the ability to give them that right now,” says prostate cancer researcher Srinivasan Yegnasubramanian. He believes if physicians were able to remove any doubt, it might change minds and significantly improve outcomes for men. He is working to create an accurate test that could be applied to blood or urine and provide clear biological evidence to distinguish aggressive prostate cancers from the slow-growing type, which could be left alone.

A Gleason score is an excellent barometer of aggressiveness, but it is only as good as the sample, he says. In men who have a prostatectomy, it is very telling because pathologists have the entire prostate to examine. When a tumor is sampled through a biopsy, though technology has greatly improved, it is still possible to miss critical areas of a tumor that could be the key to distinguishing harmless cancers from dangerous ones. Removing this uncertainty is at the core of Yegnasubramanian’s research.

His test is based on chemical alterations to specific regions of genes. They occur without mutating DNA but can have the same effect as mutations and silence the function of important tumor suppressor genes. These changes, known as epigenetic alterations, are a signature for cancer and when they are seen or begin to increase, they can alert doctors to a growing cancer. Moreover, they are very common in prostate cancer. “Epigenetic alterations can occur more frequently and consistently than mutations in prostate cancer,” says Yegnasubramanian.
Not only do these alterations serve as signatures for cancer, they are also potential therapeutic targets. Unlike mutations, in epigenetic alterations, affected genes are not missing. Instead, they are silenced by changes in the chemical environment, so researchers have the opportunity to use drugs to revert genes back to normal function. Epigenetic signatures could be used to distinguish indolent prostate cancers from aggressive ones, monitor cancers for progression and recurrence, and to determine whether treatments are working.

In recent years, the pace of these discoveries has greatly accelerated because of a new technology known as next generation sequencing. This powerful technology has the ability to rapidly and simultaneously sequence millions to billions of DNA molecules. As a result, cancer research that used to take decades can now be completed in weeks. Yegnasubramanian is the director of the Kimmel Cancer Center’s Next Generation Sequencing Center, located in the David H. Koch Cancer Research Building.

He and his team are using this technology, in conjunction with new techniques they have developed, to profile prostate cancers and identify a panel of epigenetic markers unique to prostate cancers with high Gleason scores and another to characterize cancers with low Gleason scores. Once they identify the specific markers that brand both aggressive cancers and slow growing ones, they can adapt the technology to find them in blood and urine.

“If there is a question we can ask where genomic information can help inform who should get a particular treatment and who should be monitored, I think we can go after it,” says Yegnasubramanian. “The prostate cancer program has one of the best teams on earth to define and tackle these questions.” Though many centers are thinking about these problems, he says Johns Hopkins is uniquely positioned because of its strength in translational medicine to make progress. “We have equal strength in the clinic and the laboratory,” he says. “This is a major asset that is rarely found in other centers doing genome research. Some have the research component but do not have the clinical strength we have here. Having both, allows us to make the critical connection between what we find in the laboratory and what will truly benefit patients.”

Yegnasubramanian also is collaborating with Kenneth Kinzler, one of the world’s leading cancer genetics experts, Stephen Baylin, a foremost epigenetics expert, and nationally known prostate cancer investigators Michael Carducci and Mario Eisenberger to better understand how differences in the prostate cancer genome and epigenome have an impact on treatment outcomes. His research will help physicians make the right treatment decisions for each individual prostate cancer patient.

In prostate cancer that recurs and spreads after treatment, the first line of approach is hormone (androgen) suppression therapy—in essence cutting off the supply of hormones that are believed to be fueling the cancer. At this stage, most men will survive about four years. However, our investigators have found that there are extremes in patient survival that could provide important new clues about the disease. Some men progress rapidly and may die within the first year of their recurrence, but others appear to be cured by the hormone suppression therapy, living for years without any sign of cancer recurrence. Yegnasubramanian and team believe the reasons for these differences are hidden within the genome and epigenome of prostate cancer, and they are hoping to use the power of next generation sequencing to uncover the biological differences.

"IF THERE IS A QUESTION WE CAN ASK WHERE GENOMIC INFORMATION CAN HELP INFORM WHO SHOULD GET A PARTICULAR TREATMENT AND WHO SHOULD BE MONITORED, I THINK WE CAN GO AFTER IT.

What is different about the cancer DNA of long-term survivors versus those men who have a very rapid progression? The answer would allow clinicians to direct more intensive therapies to men whose cancer DNA predestines them to be less responsive to standard treatments and give less therapy, or stop treatment altogether, in men whose cancer DNA points to long-term remission. What they learn about the extremes of treatment responses should also help all men with prostate cancer by shedding new light on other mechanisms that could be targeted in treatment. What the investigators uncover about the genetic and epigenetic basis of extremes of therapeutic response in prostate cancer will likely reveal similar information about other cancers.

PROVING A NEGATIVE

THE OLD ADAGE, “You can’t prove a negative,” is a dilemma at the core of creating better screening and diagnostic tests for prostate cancer that limit the need for invasive procedures. How do we use scientific discoveries to prove the absence of cancer with the same certainty as we prove the existence of cancer?

Despite its problems, Brady Urological Institute Director Alan Partin and other prostate cancer experts say PSA is an invaluable tool in helping monitor men who have already been diagnosed and, even with its limitations, remains useful in the diagnosis of prostate cancer. With a little help, Partin says it could be even better.

Throughout his career, Partin collected blood, urine and serum samples from his patients and created the world’s largest prostate biorepository. It greatly advanced the understanding of prostate cancer and has been critical in his work to develop biomarker tests that could augment PSA. The tests, he says, could help diagnose prostate cancer without exposing men to repeated biopsies. PSA detects cancer but it also detects a lot of other things. “We need a test that when it’s negative, we know the patient is OK. When it’s positive, we want to be confident that it’s truly positive. We don’t want to continue doing four biopsies to find the one cancer we’re looking for,” says Partin, who is the David Hall McConnell Professor of Urology.
A positive PSA means only that a man could have prostate cancer. Currently, the only way to know for sure is to biopsy the cancer, a process in which a needle is guided by ultrasound, and more recently MRI and other imaging technologies, through the rectum into the tumor.

While Johns Hopkins cancer researchers and engineers have led the way in developing new technologies that make prostate tumor biopsies remarkably precise and safe, many men still undergo repeat biopsies to confirm or disprove a cancer. Each biopsy carries a risk of bleeding and infection. Partin believes a new urine test based on a genetic discovery by Brady Institute laboratory scientist William Isaacs may help dispel some of the uncertainty and alleviate the need for multiple biopsies.

**IDENTIFYING WHICH MEN WILL HAVE CANCERS THAT ARE LIKELY TO BE CURED WITH STANDARD TREATMENTS AND THOSE MEN WHO HAVE CANCERS DESTINED TO RETURN AND SPREAD IS ESSENTIAL TO THE MANAGEMENT OF PROSTATE CANCER.**

Unlike PSA, this new gene-based urine test, called PCA3, only detects prostate cancer, but it too has its limitations. While PCA3 outshines PSA in terms of its specificity to prostate cancer, it is not as sensitive, so it has the potential to miss cancers. PSA, on the other hand, is very sensitive—quite good at picking up abnormalities in the prostate—including (but not limited to) cancer. Combined, the two tests compensate for the other’s shortcomings and, as a result, have the potential to very accurately detect cancer. If a man has an elevated PSA, but a biopsy did not reveal cancer, Partin says the PCA3 test could potentially serve as the final word. “If a PCA3 is negative, you can trust that the patient probably does not have prostate cancer. If it is positive, then he probably does,” Partin explains. “It adds another piece of information to help us better and more safely diagnose prostate cancer.”

Partin also is working on a test called AccuPSA to monitor prostate cancer patients following surgery for what is referred to as biochemical recurrence. The test uses new nanotechnology approaches to measure PSA values 1,000 times lower than a standard PSA test. A rising PSA without any visual tumors is considered a biochemical recurrence, and warns clinicians that prostate cancer cells may remain in the prostate and increases the likelihood that the cancer will ultimately return and spread.

Partin and team studied blood samples from 31 men who had undetectable PSA, using the standard test, for five years after prostatectomy. One-third of the men later began to have a rising PSA, and when Partin used AccuPSA on the blood samples, he found that the one-third of men with biochemical recurrence had a small but measurable rise in their PSA just three months after surgery. In the other men, 75 percent had AccuPSA levels lower than the men who recurred. The small study allowed Partin and team to determine a threshold for AccuPSA that could help them distinguish, within a few months after surgery, men whose cancer has been entirely eliminated with surgery from those who may have had some remaining cancers cells that could put them at risk for cancer recurrence in the immediate years after surgery.

Identifying which men will have cancers that are likely to be cured with standard treatments and those men who have cancers destined to return and spread is essential to the management of prostate cancer, says Partin.

**SEPARATING THE “GOOD” FROM THE “BAD”**

The complexities of managing prostate cancer go beyond the PSA controversy.

Prostate cancer experts have gotten extremely adept at separating aggressive cancers from nonaggressive cancers. The Gleason score, first established in the 1950s and later refined by Johns Hopkins pathologist Jonathan Epstein, ranks the nature of the prostate cancer on a scale of six to ten. Gleason six represents a lower-risk cancer; seven through 10 means the cancer is more dangerous. In short, the lower the number is, the better. Evaluated in conjunction with PSA (Prostate Specific Antigen) tests, biopsy results, and the size of the tumor, our experts say it does a good job guiding treatment.

**TARGETED RADIATION THERAPY**

A NEW FORM OF targeted radiation therapy, known as proton beam therapy, very precisely zeroes in on tumors, increasing the damage to cancer cells, while minimizing radiation exposure to healthy tissue and organs. Its precision and safety has improved radiation treatment and become the standard of care for pediatric cancers, tumors of the brain, spine and eye, and cancers of the lung, head and neck, and bone (sarcoma). The Kimmel Cancer Center is currently developing plans for a proton beam facility on its Washington, D.C., campus to provide care for patients with these types of cancers and also will be one of the few centers embarking on evidence-based research to determine other cancers best treated by proton beam therapy.

There is growing concern among prostate cancer clinicians and scientists because the most commonly proton beam-treated cancer is prostate cancer, and there are currently no research studies or findings to support it. Kimmel Cancer Center Director William Nelson and Radiation Oncology Director Ted DeWeese, both prostate cancer experts, are among the concerned, and they are committed to gathering the needed research-based evidence to prove, or disprove, its benefit. One of the first research projects at the Kimmel Cancer Center proton beam facility will be the important basic science and clinical studies that will help resolve the scientific controversy surrounding the use of proton beam therapy for prostate cancer.
As one of Hopkins busy prostate cancer surgeons at Johns Hopkins, Edward Schaeffer has observed first hand that while many of his patients are cured with surgery, some of them inexplicably have their cancers return. In his laboratory, he is working on ways to identify these patients and to develop new treatments to prevent the cancer’s return.

To decipher clues about the abnormal cell growth that leads to prostate cancer growth and spread, Schaeffer identified and focuses on a group of genes that regulates and controls normal prostate development. He postulated and subsequently showed that genes that control the movement and invasion of prostate cells during normal prostate development, become reactivated in prostate cancers. Schaeffer’s work has not yet revealed the triggers to turn these invasive genes back on, but he has found that the molecular process is linked to the most aggressive prostate cancers. This promising finding allows him to not only pinpoint those patients whose cancers are destined to return after surgery, but it also reveals a potential new target for treatment.

Schaeffer's laboratory team, led by Paula Hurley, is particularly interested in a gene known as SPARCl1, which can accurately predict whether a seemingly localized tumor will return and spread within a few years after surgery. The normal prostate has high levels of SPARCl1 expression, which holds cells in check, preventing them from migrating and moving around. Low levels of SPARCl1 allow cells to move well, serving as a biological red flag that the cancer will return with a vengeance.

Currently, Gleason Score is used to identify more aggressive prostate cancers. For example 30 percent or more of patients with a Gleason Score of seven or higher are at highest risk of having their cancers return. Unfortunately, there is currently no way to differentiate the patients who are cured with surgery from those whose cancer will recur. Measuring SPARCl1 expression at the time of surgery seems to provide the answer. In addition, Schaeffer’s research indicates that SPARCl1 could also play a role in predicting tumor recurrence in a number of other tumors, including bladder, breast, colon, rectum, tongue, lung, skin, and ovarian cancers.

Schaeffer is now working to decipher the specific mechanism that controls the gene in hopes of developing a treatment that can reset SPARCl1 to normal and prevent cancers from returning.

THE CASE FOR OPEN AND CLOSED

The Da Vinci robotic surgical system has made minimally invasive surgery a household word and has become a favorite marketing tool of community hospitals around the country. The da Vinci system boasts smaller incisions, less pain, shorter hospital stays, and shorter recovery time for patients. In certain instances, this is true. For prostatectomy, however, not everyone agrees. Prostate surgeons—like Alan Partin, H. Ballentine Carter, Edward Schaeffer, and the many other urologists who learned how to do prostatectomies by training under its pioneer Patrick Walsh, the undisputed paragon for how it should be done—do not need the assistance of da Vinci. On the other hand, robots can be quite helpful and sometimes make it possible for surgeons who do not have the skills to perform a Walsh-style open procedure to perform prostatectomies.

When it comes to prostate cancer, men may have a difficult time distinguishing good marketing from good medicine. Patients hear advertisements about one machine or another, and they think if their doctor does not use it, he is not practicing good medicine, warns John Wong, a Kimmel Cancer Center medical physicist who has invented several cancer-related devices. Many claims, he says, are made with no scientific evidence to back them up.

CHOLESTEROL DRUGS

GOOD FOR HEART DISEASE AND PROSTATE CANCER

Population studies at Johns Hopkins have shown that men on cholesterol-lowering drugs known as statins have a greatly decreased risk of developing advanced prostate cancer. Physician and scientist Phuoc Tran has gone back to the laboratory to figure out why. He suspects that these drugs block the activity of an important cancer-growth-promoting gene known as c-myc, and he proved in laboratory studies that high-dose statins, in fact, reduce c-myc activity. Now Tran, a radiation oncologist and expert on the c-myc oncogene, has initiated a clinical trial in collaboration with urologist Edward Schaeffer to verify in prostate cancer patients what he observed in the laboratory. If he confirms his findings, it could open the door to treatment strategies that could improve surgery or radiation therapy outcomes. Similarly, statin-based prevention approaches could lock prostate cancer in a nonthreatening stage and potentially stop it from occurring at all.
Partin agrees, saying that Johns Hopkins always evaluates new approaches from an evidence-based scientific standpoint. “We were using the da Vinci robot long before it was famous,” says Partin. “But, we take marketing and profits out of the equation and look at what really works the best for patients.”

Investigators in the Johns Hopkins Center for Computer-Integrated Surgical Systems helped develop some of the technology used in the da Vinci system, which employs robotics, sensors, imaging devices, and guidance systems to interface and assist surgeons when operating. Brady Urologist and biomedical engineer Mohamad Allaf works with these scientists and is director of minimally invasive and urological robotic surgery. Johns Hopkins was one of the first medical institutions to integrate robotics into urologic surgery, and Allaf is considered one of the world’s leading experts. He travels around the globe demonstrating and training other surgeons in robotic prostatectomy, nephrectomy (kidney) and other urological operations. Like the other Brady surgeons, Allaf is as skilled at open procedures as he is at robotic approaches, but with the continuing demand from patients for minimally invasive procedures and his work innovating the next generation of robotics in medicine, it is his focus.

In terms of prostatectomy, Partin says it’s a draw. Studies show that open procedures and robotic procedures, when performed by trained surgeons, are equally good and there is really not much difference in pain or recovery.

Training is key. Patients need to understand that the robot is not as important as who is operating the robot, says Schaeffer. Johns Hopkins urologists are probably the best in the world at both open procedures and robot-assisted surgery, he says. Patient demand supports this contention. Johns Hopkins urologists are the most sought after, performing hundreds more prostatectomies than any other hospital in the world. Their record is stellar, getting all of the visible cancer 90 percent of time while also preserving sexual and urinary function. Schaeffer says he finds that some men prefer the minimally-invasive prostate surgery approach, so unless the tumor is large and bulky or has other characteristics that demand an open procedure be performed, he usually leaves the choice up to the patient. This is where the skill of the Johns Hopkins urologists, experts at both types of surgery, makes a difference. They are not limited to one or the other, so they can select the approach that is best suited to each patient’s individual cancer.

HELPING PATIENTS MAKE THE RIGHT DECISION
Johns Hopkins prostate cancer experts have pioneered therapies, diagnostic tests, imaging techniques and basic science discoveries. However, what Schaeffer and his fellow Johns Hopkins urologists and oncologists take the most pride in is providing personalized treatment plans for each patient, whether it is surgery, radiation treatment, hormone therapy, active surveillance or a combination of these approaches.

NO SMOKE
A GOOD REASON TO QUIT; A GOOD REASON TO DIET
CORINNE JOSHU, the Martin D. Abeloff Cancer Prevention and Control Scholar-in Training, was looking for straightforward lifestyle remedies that could decrease the risk of recurrence in men who had surgery for prostate cancer and whose cancer had not spread. She found that men who were smoking one year after surgery doubled their risk of their prostate cancer coming back. Former smokers and nonsmokers had no increased risk. Joshu says that smoking causes cell damage that triggers the growth of new cells to replace damaged cells. It’s possible that this process sets in motion genetic changes that facilitate the return of the prostate cancer.

Joshu also looked at weight change from five years before surgery to one year after. She found men who gained five or more pounds (10 to 11 pounds on average), after surgery also doubled their risk of cancer recurrence when compared to men who maintained their weight. It didn’t matter if they were normal weight or overweight to begin with. It was the act of gaining weight that seemed problematic. Joshu is working with researchers to figure out why. “If you’re gaining weight, you are in the process of active growing. Perhaps this growth-promoting environment allows evasive tumor cells to set up shop and cause a cancer recurrence down the road,” she says.

With support from the Abeloff Scholars program and the Maryland Cigarette Restitution Fund, Joshu is investigating precisely how these lifestyle factors contribute to prostate cancer progression.

“On a day-to-day basis, our bodies are trying to fight the outside world,” explains investigator Michael Carducci, who is collaborating with Joshu on the study. “Internally things are getting turned on to combat these exposures. The more you can limit these forces by not smoking and maintaining a healthy weight and diet, the easier you make it on your body.” •
Schaeffer, medical oncologist Charles Drake, and radiation oncologist Danny Song co-direct a clinic where patients from around the world come to have their prostate cancer scrutinized by leaders in the field. Some men have localized disease and are uncertain about what is the best treatment for them. Others have more aggressive cancers they have been told are not treatable. About one quarter of the patients who come to the clinic have a change in the grade or stage of the cancer, once examined by the Johns Hopkins team, which include radiologists and pathologists, like Jonathan Epstein, the world’s most sought after prostate cancer pathology expert. Most of the time, patients get better news than what they were initially told. By the end of the day, the crack team will have laid out for them treatment options and plans.

“We offer a service based on our extensive experience that delivers the treatment best suited to each patient,” says Schaeffer. “People come to our clinic after being told they need surgery and are relieved to find out we can offer them an alternative to surgery. By the same token, we have men who come to our clinic because they have been told they cannot have surgery, and we cure them,” he says. He recalls one patient, in particular. He was 47 years old and had been told his cancer was incurable. He came to the prostate cancer clinic, where Schaefer and team worked out a plan that included surgery and radiation therapy. That patient continues to do well today.

Why can Johns Hopkins experts offer patients treatments that other hospitals cannot? “The technical experience is better here than anywhere else in the world,” says Schaeffer. “But just as important, we know how, when, and to whom to employ this expertise. This personalized approach is the essence of the Prostate Multi-D Clinic, and we do it better than just about anyone.”

SCIENCE, POPULATIONS AND PROSTATE CANCER

Elizabeth Platz is a population scientist. She uses questionnaires, records, and biospecimens to observe men—what they do and what they do not do—and applies what she sees to prostate cancer. For example, her landmark study of nearly 5,600 men aged 55 and over, found those with normal or low serum cholesterol had a 60 percent lower risk of developing aggressive (high-grade) prostate cancer than men who had borderline and elevated levels. In an earlier study she observed that men who used cholesterol-lowering drugs known as statins had a decreased risk of developing aggressive prostate cancer.

There seemed to be a link—men with lower cholesterol and men who used cholesterol-lowering drugs, improved their prognosis, decreasing their risk of developing a more aggressive form of prostate cancer. To determine why she finds the things she finds, Platz, the Martin D. Abelloff Scholar in Cancer Prevention and Control, turns to her laboratory and clinical science colleagues to unearth answers, and vice versa.

Marion I. Knott Professor and Director of the Kimmel Cancer Center William Nelson and investigator Srinivasan Yegnasubramanian worked with researcher Jun Liu, who has constructed a repository of more than 3,000 FDA-approved medicines, in hopes of identifying some commonly used noncancer drugs that might work against prostate cancer. When they screened human prostate cancer cells against the drug library, two of the top 15 hits were statin drugs. One was digoxin, an older drug that, in the past, was commonly used to treat congestive heart failure.

Scientists are looking for new ways to contain the cost of drug discovery, an enterprise in which a billion dollars can be spent to bring one drug to market. The promise of most drugs, or lack thereof, is usually only realized after years of costly research. As director of a cancer center, Nelson understands cancer researchers have to do better. He envisioned a two-stage approach to see if what he, Yegnasubramanian, and Liu found in the laboratory studies of prostate cancer cells would be supported or refuted by what Platz observed in men.
Damon Sings

Former Temptations member DAMON HARRIS reflects on his 14-year battle with prostate cancer.

by Valerie Matthews Mehl
TODAY, WHEN DAMON HARRIS LOOKS AT OLD 1970s PHOTOGRAPHS of himself performing as a member of the vocal group the Temptations, he does not simply reminisce about his twenties and the heyday of his career. Instead he reflects at what the camera lens does not reveal. Beyond the spotlight and celebrity, he marks the beginning of his battle with prostate cancer.

Damon was diagnosed with advanced prostate cancer in 1998 at just 47 years old, but he has since learned from his doctors that this slow growing cancer had probably started forming 20 years earlier. At the time the photos were taken, there were no symptoms to alert him to the invisible genetic miscues occurring within his body and giving rise to the cancer cells. He was unaware that as an African-American man with a family history of prostate cancer, he was at increased risk for the disease and at risk for developing it at a younger age. His father died when Damon was just 25. However, Damon did not realize until he read the death certificate that his father died from prostate cancer. “I saw my Dad die. I saw him suffer, but he never talked about it,” says Damon. It was indicative of the time. “Black men didn’t talk about prostate cancer,” he says.

Flash forward 15 years, and perhaps things are not that different. Damon recalls living with symptoms for five years before going to the doctor. Like his father before him, he suffered in silence. He convinced himself that the pain he was experiencing was just a normal part of middle age. “I was stretching and putting cold compresses on my pelvis trying to relieve the pain.”

He was living in Philadelphia at the time. He had spent the last decade touring internationally as a solo artist and had decided to relocate to Nevada to work with a singing group who was performing at a hotel in Reno. He enrolled at the Reno campus of the University of Nevada to continue his studies in music education.

A few years later, the pain returned, and now it was intolerable. Dr. Carol Scott at the University’s Health Center convinced him that he needed a PSA test and prostate exam. The results were unmistakable. Damon did not just have prostate cancer; he had bad prostate cancer. His biopsy and other tests revealed that the cancer had already spread.

As a young man, he had dreamed of living in Reno. His plans did not include a diagnosis of prostate cancer. Within days of his diagnosis, he went to the Reno chapter of the American Cancer Society (ACS) for what he calls his “crash course in Cancer 101.” The local ACS director asked Damon to be a coordinator and facilitator for its Man-to-Man program, an education and support program for men with prostate cancer. He spoke to many groups. The black population in Reno was very small, so he was the only black man in the room. “It was an eye-opening experience for them and for me,” recalls Damon. “It was an unusual encounter for us all, but despite the obvious differences, we were brothers. The disease brought us together.”

The ACS sent Damon around the country to attend national conferences and other prostate cancer events. His “crash course” also led him to another prostate cancer group. An internet search turned up a patient-led advocacy group called the National Prostate Cancer Coalition (NPCC). The urologist Damon saw in Nevada did not offer much hope, but a contact he made while attending the group’s annual meeting in Washington, D.C., did. Damon became friends with Judge Ralph Burnett, himself a newly diagnosed prostate cancer patient and the organization’s chairman at the time. The judge was a champion of increased research funding and education for men diagnosed with the disease. “He was genuinely concerned for me and told me I needed to see his doctor, Dr. Bill Nelson at Johns Hopkins,” says Damon

Damon followed Judge Burnett’s advice and made an appointment to see Dr. Nelson. Damon’s prostate cancer was too advanced to be cured with surgery, but hormone drug therapy could—and did—keep it in check. The treatments have not been without their side effects, but he has been well enough to continue performing. A highlight for him was performances last year at the Kimmel Cancer Center’s Cancer Survivor’s Day celebration and Art of Healing Program. He sang “We Shall Overcome,” and was joined by patients in a moving and spontaneous display of courage and solidarity that, while emotional for all who witnessed it, was probably only fully appreciated by those fighting cancer. “I was moved to ask patients to come stand with me because I could identify with what they were going through,” says Damon.

“Though we all have different experiences in fighting our cancer, we are also joined together by a similar experience. I was the one on the stage singing, but my voice was speaking for all of us.”

For the first time, Damon has written, arranged, and produced his own music. He recorded “You are My Woman” last spring at Johns Hopkins Peabody
when he began experiencing symptoms, he still would not have gone to the doctor. “Sadly, the thought of having a DRE [digital rectal exam] is scarier for many men than dying,” he says. “I’ve heard men say, ‘I’ll die before I do that,’ and I want to do anything I can to make sure that doesn’t happen.”

To help get his message out and provide support to African-American men, Damon has formed the Damon Harris Cancer Foundation and is developing an associated website that links African-American men to African-American urologists. It was an idea that came to him while attending a conference through the American Cancer Society. A chance meeting with acclaimed black urologist Janice Arnold made him think, “Maybe some black men would be more willing to get screening examinations if they could go to an African-American doctor. The history of black people in America is such that some black men are understandably reluctant to listen to white doctors. The trust is missing,” he says. “But, we can’t quit trying to get the message out.” His goal is to make sure every man has an option that works for him. If going to a black doctor is more comfortable, he wants them to know where to find one. “Information is key,” says Damon. “People need to make their own decisions. The decision I made may not be the right one for someone else, but I try to help make sure people at least have the facts, like ACS and the NPCC did for me.”

TO HAVE CANCER IS NOT TO DIE. TO HAVE CANCER IS TO LEARN HOW TO LIVE.

First and foremost, he hopes that sharing his story and providing connections to doctors will encourage men to discuss prostate cancer with a doctor before they have symptoms. “Race is a sensitive issue. The media are afraid to talk about the problems of prostate cancer in African-American men. There is a hesitation to emphasize race, but we can’t be afraid to say that in America prostate cancer is different in African-American men,” says Damon. “It’s a fact, and if we are reluctant to talk about it, we are never going to get this problem under control.” While he hopes for a greater impact, Damon says if his work gets just one man to talk to his doctor about prostate cancer, he feels he’s made a difference.

Sharing his journey and his experience at Johns Hopkins is one way he hopes to accomplish that goal. “Johns Hopkins is the greatest hospital in the world,” says Damon. “I’m not a wealthy man as many would expect or imagine, so it’s not my celebrity that has earned me the best treatment. In my experience, it’s representative of what Johns Hopkins delivers to each and every patient,” says Damon.

Dr. Nelson points out that Damon Harris is a perfect example of someone who may have benefitted from screening. With so much attention focused on over-screening men, Dr. Nelson wants men to understand that screening is not bad; screening the wrong people is bad. He says, “What we need to do is target prostate cancer screening to the right men, those who will benefit, and away from those who will not.”

Even though Damon missed the opportunity for early detection and a cure, he still considers himself a prostate cancer success story. At 62, he has lived with advanced prostate cancer for 14 years. He attributes his survival to a combination of “his doctors’ work and God’s grace.” He says, “The Kimmel Cancer is a second home to me. I feel certain that if I had not come to Johns Hopkins, I would not be alive now.”

Recently, the cancer has started to grow again, and he is beginning radiation treatment to knock down some painful tumors pressing on the nerves in his hips and spine. He also is eager to begin treatment with a new FDA-approved drug called MDV-3100. He continues to be impressed with the combination of approaches his doctors have used to keep his cancer under control. When drug treatments have failed, he says, radiation therapy has stabilized the cancer.

Despite it all, Damon feels blessed. He does not ask why or wonder what if. “I was given the gift of voice, and I am being allowed to use that voice and to be heard through my music and my experience with cancer to help other people,” says Damon. “To have cancer is not to die,” he says. “To have cancer is to learn how to live.”
PRO ANTIANGIOGENESIS

ANTIANGIOGENESIS: IT’S A LONG word to describe cancer treatments that work by cutting off the blood supply that tumors need for nourishment and growth.

Clinician-scientist Hans Hammers is hoping to take what he’s learned from success using antiangiogenesis therapies for kidney cancer to better treat prostate cancer, where antiangiogenesis has not worked so well.

Traditional chemotherapy does not work at all in kidney cancer. The kidney, adept at flushing out toxins, gets rid of anticancer drugs before they can go to work. Antiangiogenesis discoveries totally changed the way kidney cancer is treated, Hammers says, and every antiangiogenesis agent they use targets a single pathway, known as VEGF.

VEGF helps tumors develop the blood vessels they need to grow and spread. Targeting the pathway with treatment tears down vessels that have already formed, and blocks the development of new ones, and shrinks kidney cancers by half.

Hammers believed he should be able to achieve the same response in prostate cancer, but these cancers were inexplicably resistant to the treatment. Animal studies funded by the Maryland Cigarette Restitution Fund allowed him to trace the resistance to very primitive cells that march away from the tumor and begin growing elsewhere in the body, a process known as EMT. Hammers examined stable, treatment-responsive kidney and prostate cancers. When he altered tumor cells to initiate EMT, the cells became resistant to antiangiogenesis treatment. “What we see in a high Gleason grade, which represents the most aggressive prostate cancer, is essentially EMT occurring,” says Hammers. “Gleason rating is a depiction of EMT.”

Hammers is working to decipher the specific cellular mechanisms involved in EMT and identify targets for treatment. He believes targeting EMT could make antiangiogenesis treatments effective against prostate cancer and potentially many other cancers as well.

Paltz and her epidemiology colleagues followed nearly 50,000 men and compared digoxin users to nondigoxin users and found men who took the drug had a 25 percent lower risk of developing prostate cancer than those who did not. Now, the team had laboratory evidence that digoxin halted prostate cancer cell growth and a population study that found a significantly decreased risk of prostate cancer among men who took the drug.

It was unlikely a fluke. Getting the same findings twice, once in the laboratory study and then in the population study, removed the likelihood that the results they were finding occurred by chance. Prostate cancer experts at Johns Hopkins and around the world deemed Nelson and team’s laboratory/population approach quite smart. Combining the two types of research helped ensure that the investigators were not wasting time or limited resources pursuing a dead end.

With good evidence that the heart drug truly has anticancer properties, the researchers are now working to figure out exactly how it works in prostate cancer.

Digoxin has a number of side effects, but Nelson says if they figure out how it works, they can develop or identify another drug that can safely treat or even prevent prostate cancer.

A TRAIN RIDE AND TELOMERES

Riding the train together on the way back from a prostate cancer meeting in 2004, researchers Alan Meeker, Angelo De Marzo, and Elizabeth Platz enthusiastically planned the next phase of their breakthrough prostate cancer study.

De Marzo is among the world’s best prostate cancer pathologists, but what he couldn’t figure out was why men with seemingly similar cancers under the microscope often had very different outcomes in the clinic.

What was different about their cancers, De Marzo, Meeker, and Platz wondered. If they could figure it out, perhaps they could develop treatments that would benefit all men. In this new age of molecular medicine, was there something else beyond currently used pathology indicators—stage, Gleason grade, and PSA—hidden within the cancer cell that could determine prognosis?

It was 2004, four years before Johns Hopkins researcher Carol Greider would win a Nobel Prize for her research on chromosome ends known as telomeres. Similar to the plastic coverings that shield the ends of shoelaces from damage, one can think of telomeres as the protective end caps of chromosomes. Building upon Greider’s growing body of work, Meeker and De Marzo received a Maryland Cigarette Restitution Fund grant to study telomere length and its potential link to cancer. As normal cells age and divide, some of the telomere DNA is lost and telomeres get shorter and shorter. Normal cells monitor the length of their telomeres and initiate cell death if they get too short. It was already well recognized that telomeres were shorter in cancer cells than normal cells. They wondered whether this monitoring system breaks down in cancer cells and whether assessing telomere length could be a marker for prostate cancer aggressiveness. In preliminary studies, the investigators examined precancerous prostate lesions and found much shorter telomeres.

This finding was the focus of their conversation as they sat huddled on the train outlining the next step in their research. Their excitement about studying telomere length to see if it could tell them something new about prostate cancer aggressiveness and prognosis did not go unnoticed by their fellow passengers in the “quiet car.” Unaware of their cancer discovery and unappreciative of the chatter, Meeker, De Marzo, and Platz were soon asked to find different seats on the train.

With funding from the Department of Defense, they began to study the ideas they discussed on the train ride. They examined telomere length in the chromosomes of human prostate cancer cells and nearby cells from the stromal or connective tissue surrounding the prostate that had been preserved in a special specimen bank at Johns Hopkins. Cell by individual cell, a research fellow painstakingly circled every relevant cell on digital images of tissue that were stained with a fluorescent dye to mark the telomeres. A computer-
ized method quantified telomere length, the number of short telomeres, long telomeres, and mix of both. Meeker and De Marzo developed the approach to complete such a thorough and comprehensive examination. No research team had ever looked cell by cell, opting instead to study bulk tissue, primarily because it was a simpler and less labor-intensive process. Meeker recognized they could miss something doing it that way. In fact, what they found could only be deciphered by a method like the one Meeker and De Marzo developed. The research team was surprised to learn that it was not short telomeres in the cancer cells that seemed to matter but rather the variability in the length of telomeres from cancer cell to cancer cell that influenced the outcome of men with prostate cancer. The unconventional approach was dead on. “If we had done it the way everyone else does it, we would have never found this,” says Platz. “Some were shorter. Some were longer, but it was the variability from cell to cell that predicted lethal prostate cancer, and it could be found only by looking at each cell.”

Variable telomere length in prostate cancer cells and short telomere length in the nearby stromal cells translated to a much higher risk of dying from prostate cancer. Prostate cancer cells with less variability in telomere length and longer telomeres in the stromal cells marked a less aggressive form of prostate cancer. When they separated the samples based on these characteristics and referenced back to the actual patients from whom they were obtained, the investigators found that only one man in the lower-variability/longer telomeres group died from his cancer compared to 20 in the higher-variability/shorter telomeres group. “The marker gives us information and detects high-risk disease independent of other screening and staging tests,” says Platz.

With support from the Department of Defense, the National Cancer Institute Prostate Cancer SPORE grant, and the Johns Hopkins Prostate Advisory Council, the research team is now working to develop an automated approach to speed up the burdensome process of measuring telomere length in individual cells.

The team sees many potential applications for their discovery. “Maybe there are subsets of men in whom we can use telomere length to predict response to treatment and determine precisely what treatments will work for each patient,” Platz says. Examination of telomere length could also be used to help identify men whose cancer is likely to progress and would not be good candidates for active surveillance. Conversely, it could be used to provide more evidence of low-risk disease and give reassurance to men who are enrolled in active surveillance. “Treatment has side effects. We don’t want to give it to a man who does not need it or when we know it will not help,” says Platz. “Telomeres may be a marker we can use to individualize our prostate cancer therapy to maximize benefit and minimize risks and adverse affects for each patient.”

**WONDERING ABOUT THE WONDER FRUIT**

The idea for Michael Carducci’s clinical research of the pomegranate fruit actually came from the Kimmel Cancer Center’s benefactor and namesake Sidney Kimmel. A pomegranate product manufacturer was widely touting a UCLA study that seemed to indicate that the fruit had prostate cancer-fighting properties. Kimmel wanted his cancer center to figure out if it was true, and Center Director William Nelson thought Carducci was just the person to sort it all out.

Carducci, the AEGON Professor in Prostate Cancer Research, decided not to limit his work to pomegranates. There are a range of natural products marketed for prostate health, and Carducci decided to follow Kimmel’s lead and conduct studies to look for real, scientific evidence that these natural ingredients had an effect on prostate cancer cells through clinical studies. He has recently completed studies of pomegranate and is now beginning to look at Vitamin D and soy protein as well as muscadine grapes skins.

The UCLA study found that pomegranate juice slowed PSA doubling time in men who had prostate cancer, an indication that pomegranates could be slowing the progression of the disease. Carducci wanted to see if he could replicate these results and also determine if the amount a person consumes makes a difference. For his studies he used POM Wonderful pomegranate extract capsules because the product is 100 percent pome-
DONALD COFFEY WAS RAISED IN THE HILLS OF BRISTOL, TENNESSEE IN THE 1930s. His father ran a service station. Neither of his parents finished high school. He struggled in school himself—repeated grades, was asked to leave his first college, and was rejected by 20 graduate schools. He never heard of Johns Hopkins or Baltimore, and never knew a doctor or anyone with cancer, but after praying and meditating, he had what he describes as an overwhelming desire to study cancer.

The unlikely journey that brought him to Johns Hopkins was far from easy, but as Johns Hopkins leadership would soon recognize, one of academia’s worst students was an astute learner and even better teacher. Coffey became one of Johns Hopkins foremost experts in prostate cancer and one of its most sought after professors.
In more than 50 years at Johns Hopkins, Coffey has racked up a long list of accomplishments. Many of the accolades are as unconventional as the man. He served as acting chair of the Department of Pharmacology without ever taking a course in pharmacology. With no medical degree, he helped found the Cancer Center in 1973 with its first director Albert Owens and then ran it in 1987, and served as President of the American Association of Cancer Research from 1997 to 1998. The jovial, spectacled, southern-speaking Ben Franklin look alike is a one-of-a-kind, and his story is as much about cancer research as it is about the human spirit.

The early research of Donald Coffey was in many ways the bedrock on which modern genetic and epigenetic discoveries at Johns Hopkins were built. In 1974, he turned the research world upside down challenging the popular thought on how DNA was copied. At the time, little was understood about DNA and genes. Most researchers were interested in understanding what it was and what was recorded on it. Not surprising, Coffey had a different idea. He was interested in the structure of the tape and how it was organized in the nucleus. He decided to look at the core of the nucleus. It was a revolutionary idea. Most scientists believed there was nothing inside the core.

Popular thought was that there was no single place in the cell where DNA was copied. Instead, scientists hypothesized that DNA was like a tape and was replicated by a moving recording head, of sorts, which ran along the stationary tape. Coffey disagreed. He believed the core of the nucleus was where DNA was copied and that the tape-like DNA strands, a yard long, were coiled tightly inside the cell nucleus.

For those born in the digital era, the tape cassette and recorder analogy seems outdated, but one has to remember this research was occurring in the 1970s.

Coffey recognized that a doubting scientific community would not believe it unless they could see it, so they showed what all of it looked like through pictures and

[THE COFFEY WAY]
“DON’T ASSUME ANYTHING YOU CAN’T PROVE.”

With a $500,000 no-strings-attached cancer research grant from Bristol Myers, Coffey brought together two young up-and-coming unknowns in the field of cancer research, Drew Pardoll, an M.D.-Ph.D. student, and Bert Vogelstein, who Coffey calls the only true genius he’s ever met.

Pardoll theorized that rather than using one mobile recording head, the DNA tape was instead copied at thousands of fixed sites along what they dubbed the nuclear matrix. Coffey explains, “The nucleus has a skeleton to it. That’s the nuclear matrix. Attached to that skeleton are recording heads, the machinery that replicates DNA. The DNA is organized in thousands of loops moving through these heads.” Vogelstein used a series of calculations, which Coffey describes as too complex to translate, and showed that Pardoll’s model could work.

[THE COFFEY WAY]  
**THE EXPERIMENT THAT DOESN’T COME OUT THE WAY YOU THINK IT SHOULD IS THE ONLY EXPERIMENT THAT IS REALLY GOING TO TEACH YOU SOMETHING NEW.**
scale models. Coffey recalls, “Ken Pienta and I went to Sears and bought a jigsaw, and we built an award-winning scale model 175 feet long of a relaxed single loop of DNA magnified 25 million times.”

Another scale model, this one just four feet long, was constructed to illustrate the super-coiled loops of DNA.

What does all of this have to do with cancer? For that, Coffey, the professor known for using Slinkys, soap bubbles, soda cans, and a 175-foot long replica of a DNA loop to illustrate a point, turns to the cassette recorder. He pops an audiocassette tape into a tape player and pleasing sounds of Johann Strauss’ Blue Danube waltz begin to play. Without warning, it is interrupted by the Rolling Stones singing Get Off of My Cloud. Unexpectedly, the tape begins once again to play Blue Danube. “This is cancer,” says Coffey. “Cancer is like your body’s genetic tape playing the wrong song at the wrong time,” explains Coffey. “The tape is all mixed up and contains errors. Cancer is a problem of uncontrolled cell growth and differentiation, and I want to know what tape is played and when. Pieces of the tape are in wrong place, and there are errors in what is playing. Songs are played at the wrong time. Embryonic songs are played when they should have been turned off.”

Baylin and William Nelson showed that the coils and loops touch and interact with many gene sites, creating a structure that turns off tumor suppressor genes.

Still, at the time of their discovery, the notion of a matrix was met with skepticism. “It was amazing how these young people here could prove this stuff against the greatest labs in the world,” says Coffey. Suddenly scientists at MIT and Princeton were doing similar experiments.

Coffey was not blindly enamored of the work that came from more prestigious academic institutions nor was he disregarding of the observations of everyday folks who learned their trade on the job and not in the classroom. He was as comfortable conversing with the janitor as he was with the CEO. This not only made him a fine human being but also a stellar scientist. Coffey was interested in solving problems, and he was not someone motivated by notoriety or celebrity.

He tells of a job he had when he was in college working as a chemist for the North American Rayon Company in Tennessee. They were having a problem with lines that carried acid used in the production of rayon. The acid would back up and spill all over the floor. Coffey was charged with finding out what was causing the problem. He talked to everyone he could think of, including Big John, a laborer who worked in the basement of the building. Big John tipped him off to a vibration in a machine that started about 20 minutes before the breakdowns occurred. This observation led Coffey to the cause of the problem.

Coffey believed that to find answers, one first had to ask the right questions. “He liked to gather everyone’s ideas. He made people feel like no idea would ever be looked at as being stupid,” recalls Pardoll. Coffey and Big John became instant legends at the North American Rayon Company, and his boss there, a Johns Hopkins alumnus, inspired him to go to Baltimore. He boss told Coffey, “You’ll have to work your way in, but they’ll take care of you. When you hit the ball they don’t care who you are.”

“I was a C student from East Tennessee State University, and now I was planning to go to Johns Hopkins,” says Coffey. (Before Tennessee State, he attended Kings College. The college president suggested he leave after hiring a plane to drop political leaflets, some of which got wet and dangerously fell to the earth like a cinder block. Years later, Kings College gave him an honorary doctorate.)

Coffey discussed it with his wife Eula, and they agreed they should move to Baltimore. By day, Coffey worked at Westinghouse designing radar antennas. In the evening, he took classes and got his foot in the laboratory door by washing glassware for graduate students. After receiving a glowing reference from his former employer at North American Rayon, the School of Medicine hired him to work evenings in the urology lab. A year later, in 1959, with no graduate degree, he was named the acting director of the Brady Urological Research Laboratory. “The starting salary was $5,000. I was making $18,000 at Westinghouse, but I knew I wanted to do cancer research.” After a year of running the lab, he was accepted to the School of Medicine’s graduate program in Physiological Chemistry.

Coffey earned his Ph.D. at 33. By then, he had already been a chemist, an engineer, a laboratory director, and prostate cancer researcher. Everybody wanted him, and Professor Paul Talalay hired him to the Pharmacology Department faculty. Soon thereafter, Professor William Scott invited him to join the faculty of the Urology Department. Coffey’s meteoric rise from his self-described role as “chief bottle washer” to become the Catherine Iola and J. Smith Michael Distinguished Professor of Urology; professor of Oncology, Pharmacology and Molecular Sciences, and Pathology; and a member of the professional staff of the Applied Physics Laboratory seemed right out of a Hollywood movie.

In fact, despite his academic struggles, Coffey was a perfect fit for Johns Hopkins. He believed that much could be learned if
people from different disciplines would just get together and talk about a problem. “People like to visualize a disease as one thing wrong. Like, there’s a wire loose in car, but it’s never just one wire in a car. By the same reasoning, it takes multiple steps to form a cancer cell. There’s an aging phenomenon associated with it, a genetic phenomenon, and a whole bunch of environmental and epigenetic factors. Man, I hate to tell you how often people from all those different fields don’t get together in science,” says Coffey.

[THE COFFEY WAY]
“GENERATE MORE THAN ONE CONCEPT TO EXPLAIN YOUR DATA, THEN GIVE ALL THE POSSIBILITIES YOUR EQUAL ATTENTION AND EFFORT. YOUR PET IDEA WILL USUALLY TURN OUT TO BE JUST THAT.”

For Coffey, neither the classroom nor the laboratory ever closed. In the hallways of the Brady, in his office over high tea, or in a conference room, Coffey could be found fostering collaborations and inspiring innovative ideas about cancer. It was not unusual for these discussions to last long after business hours. The next morning, equations and notes jotted across blackboards were evidence to the lively discussions that had occurred the night before.

Coffey, who suffers from dyslexia, profoundly understands that everyone learns differently. The disorder that caused him to struggle as a student helped make him one of the world’s greatest teachers.

Among his many revered lessons is what he calls the “Real Final Exam.” In it, he extols several time-tested principles.

In fact, the last one is a favorite of Coffey’s who sometimes seems to espouse credit for everyone but himself. Back at North American Rayon Company, though he put all of the pieces together to solve the acid line problem, he quickly redirected credit to Big John and secured him a sizeable raise. He talks willingly and with pride about the accomplished researchers and clinicians who have come through his laboratory. Rightfully so, as the list reads like a who’s who in cancer. In addition to Vogelstein and Pardoll, it includes Kimmel Cancer Center Director William Nelson, Urology Director Alan Partin, Radiation Oncology and Molecular Radiation Science Director Ted DeWeese, and Prostate Cancer Foundation President and CEO Jonathan Simons, to name just a few.

Coffey continues to patrol the hallways of Johns Hopkins in search of new talent. He has a simple formula for finding the best and brightest. He asks people. It could be other professors or students, or even patients. He asks them, who is the smartest? Who is the best? Then, he recruits these rising stars to the fight against cancer. As the list of his recruits attests, the formula is one that works.

Coffey turned 80 on October 10, 2012, but age has done little to quell his quest for knowledge. His most recent research examines the shared traits between bacteria and cancer cells. Coffey and his collaborators believe that cancer cells, like bacteria, rely on communication and “social networking” to survive and thrive within the body. Cancer cells and bacteria use chemicals and gene pathways to override controls that tell cells how to behave, he says. He hopes that better understanding the social behavior of cancer cells—intricate cell-to-cell communication they use to grow, spread, and evade treatments—will inspire new therapeutic approaches.

[THE COFFEY WAY]
“WHEN DISCOVERIES ARE MADE, GIVE EVERYONE CREDIT. YOU WERE PROBABLY NOT THE FIRST ONE TO STUDY THE PROBLEM, NOR WILL YOU BE THE LAST.”

Coffey was also part of a team that used a testicular cancer model to prove that cancer cells that are exposed to heat are easier to kill with anticancer drugs and radiation therapy. They showed that even advanced cancers that have spread to other parts of the body could be rein in with heat. To develop it clinically, Coffey, Radiation Oncology Director Ted DeWeese, and scientists Robert Ivkof, Shawn Lupold, and Prakash Kulkarni are using small antibodies that attach to iron particles which, in turn, naturally attach to cancer cells throughout the body. When exposed to alternating magnetic fields, the iron particles vibrate enough to heat up the cancer cells so they become more vulnerable to therapies.

Coffey says these discoveries have led to a new fascination with temperature. In terms of personalized medicine, Coffey points out, temperature, as fever, is one of primary measurements used to determine whether someone is sick—and he ticks off a multitude of questions: “I am trying to understand temperature and the scientific and evolutionary reason for the precise body temperature of 98.6°. Why is it not 87° or 103°, and why does a chicken egg hatch at approximately 100°? Why is a hurricane caused by only a few degrees change in ocean surface temperature? Why does a flame form in a precise structure on a candle? And why does a woman’s temperature go up a few degrees when she ovulates? Why is the sex of an alligator and turtle decided at precisely 100°? And why does a man’s sperm not survive body temperature? Why do snowflakes form such interesting patterns? How does life form against the second law of thermodynamics of increased entropy and heat? How can this heat and temperature be used to cure infections and to treat cancer and to germinate acorns and to form the precise tree line on the mountain?”

While the answers to these questions may, for the time being, remain a mystery, one thing is certain. In the inquisitive mind of Donald Coffey, nothing changes but the birthday. His enthusiastic and continuing quest for knowledge promises to bring Johns Hopkins and the world more unexpected discoveries, unusual props, and riveting lectures.
granate. Regarding the pomegranate industry, he cautions buyer beware, as the demand for the fruit is 15 times greater than production. Many products on the market contain a very small amount of pomegranate juice mixed with blueberry, grape, acai or other juices. Carducci says pomegranate is of interest to cancer researchers because it is the highest in antioxidants, chemicals known to have cancer-fighting properties.

Carducci and his team, which includes Emmanuel Antonarakis and Channing Paller, are still sorting through their findings. They confirmed the findings of the UCLA study, also finding that PSA doubling time slowed, an indication, but not proof, that it has an impact on the progression of the disease. Moreover, they resolved the “how much is enough” issue, and showed that low doses of the extract had the same effects as higher doses. “We have to verify that the affect we’re seeing is caused by the pomegranate and not just a natural process we’re picking up because we’re watching more closely,” says Carducci. “We think that slowing PSA is good thing, but we have to prove that it actually makes a difference in patient outcomes,” he says.

Another similar study in partnership with Howard University is exploring the benefits of muscadine grapes. The skin of these large, dark-purple grapes contains two antioxidants, resveratrol, which is common to grapes, and ellagic acid, the same antioxidant in pomegranates.

Carducci hopes that their studies will lead them to alternative therapies for men whose PSA begins to rise after surgery, an event called biochemical recurrence. One option for these men is hormonal therapy, but these therapies have annoying side effects such as weight gain and hot flashes and, even more of a concern, they may accelerate heart disease. “If there is a more natural approach that would allow these patients to avoid adverse affects, it would be very exciting,” says Carducci.

TRACING THE MUDDLED GENEALOGY OF PROSTATE CANCER

IT TOOK 20 years of work, but a research team led by prostate cancer laboratory scientist William Isaacs has uncovered the genetic driver for a hereditary form of prostate cancer that tends to strike younger men. It is the first major gene finding associated with inherited prostate cancer.

“It’s long been clear that prostate cancer can run in families, but pinpointing the underlying genetic basis has been challenging and earlier studies have provided inconsistent results,” says Isaacs, the William Thomas Gerrard, Mario Anthony

JOHNS HOPKINS PROSTATE CANCER MILESTONES

- Performed the first prostatectomy in 1904 and later pioneered the anatomical nerve-sparing approach
- Developed some of the first therapeutic approaches and clinical models for prostate cancer, including the earliest form of brachytherapy, and were the first to culture human prostate cancer cells to study therapeutic targets
- Developed the first animal models to characterize the properties and types of prostate cancer; the models were sent
- Discovered the first human gene mutation in prostate cancer
- Deciphered the mechanisms for prostate cancer metastasis
- Provided the first description of the basic cellular and molecular properties of prostate cancer
- Were the first to describe the importance of stem cells in prostate cancer
- Deciphered how prostate cancer growth is regulated
- Defined hereditary prostate cancer
- Performed the first DNA methylation studies in prostate cancer
- Developed an animal model of prostate inflammation and defined PIA (proliferative inflammatory atrophy), a new model for what causes prostate cancer
- Pioneered quantitative pathology to refine staging and prognostic markers
- Developed the Partin Tables, Pound Tables and Han Tables to predict localized cancers, relapse time, metastasis and survival
- Used PSA velocity to define lethal types of prostate cancer
- Developed and clinically tested the first prostate-specific adenovirus to treat recurrent and metastatic prostate cancer
- Performed the first protein analysis of normal prostate and prostate cancer
- Developed new biomarker tests for prostate cancer
- Led the work in robotics for prostate cancer treatment
- Pioneered tumor immunology studies and developed GVAX, the first therapeutic vaccine for prostate cancer
- Identified new drug targets, PSA-activated prodrugs, and other agents
Duhon and Jennifer and John Chalsty Professor of Urology.

Isaacs’s work was inspired two decades ago by the pioneering work of Bert Vogelstein and team that uncovered genetic alterations linked to hereditary forms of colon cancer. These findings led to cancer being defined as a genetic disease and ultimately revealed the complex landscape of colon and other cancers among the general population. Unlike colon cancer, which provided inherited syndromes and early onset of disease as clues, in prostate cancer “there were no syndromes families where 25-year-olds were getting the disease, and we could study them,” says Isaacs.

It was frustrating for Isaacs because earlier studies seemed to indicate that prostate cancer had a strong hereditary susceptibility, higher than colon and breast. Where was it? Why couldn’t they find it?

It turns out that techniques that worked so well in defining the genetic culprits for colon and breast cancer did not work so well with prostate cancer. “It’s a disease that most men get,” says Isaacs. He points to volumes of books on his shelf that contain pedigrees of families where three or four families had prostate cancer. “It is the most common cancer in men. We are going to find families with multiple members who have the disease, even without a genetic component, just because it is so common.” Tweezing out which ones were genetically linked and which ones were not turned out to be a monumental task.

With other cancers, early age at diagnosis is a red flag for a hereditary link. In prostate cancer, the best determinant of early age of diagnosis relates directly to how early a person is screened. “If you have a 20 year old with a lump in her breast, you know it’s early onset,” says Isaacs. “With prostate cancer, you could have a guy diagnosed at 75 who may have had the tumor since he was 45 or younger.” It is well known that prostate cancer is a slow-growing cancer and autopsy studies done at Johns Hopkins have revealed early cancers in men in their twenties and thirties. “We wouldn’t know if a man had prostate cancer at 25 because no one screens for it at that age, and he probably wouldn’t have any symptoms that would cause him to see a doctor,” says Isaacs.

Enter PSA. Now men were being diagnosed in their 40s and 50s, and they wanted to come to Johns Hopkins to have Patrick Walsh take their prostates out because he was the only guy in the world that could do it without leaving them impotent and incontinent. Over a five-year period, prostatectomy went from a surgery rarely done to the most common surgery performed at Johns Hopkins. Walsh was asking his patients about family history, and some of them were telling him that their grandfather, father, brothers all had prostate cancer. Influenced by the late Barton Childs, a legendary Johns Hopkins pediatrician and geneticist that shaped the understanding of inherited disease, Walsh began cataloging prostate tumors to characterize a hereditary form of the cancer.

Bob Carter, a young medical student working with Isaacs and Bloomberg School of Public Health investigator Terri Beatty, asked Walsh if he could look at his first 600 patients, and using their wives as controls determined that if a man has prostate cancer or one of his brother’s has prostate cancer, the other brothers were at risk. This 1990 finding reignited the search for an inherited form of prostate cancer and the gene or genes behind it. Isaacs was intrigued.

The group put an ad in Parade Magazine seeking volunteers with a family history of prostate cancer. Within two weeks, they had 2,500 men who responded and were eager to help decipher the disease. Public announcements by General Norman Schwarzkopf, Senator Robert Dole, and financier Michael Milken about their own diagnoses with prostate cancer all inspired to bring attention and interest to the disease. “Research ticked up, but when the smoke cleared 15 years later, we still didn’t have anything particularly useful,” says Isaacs. “A few genes turned up, but their effects turned out to be small.”

Then, in the mid 2000s a new idea was being explored. Adopting the premise that humans are really all one big happy family extending from a small number of original founders, there should be a limited number of founder chromosomes in the population. Bert Vogelstein’s research revealed founder gene mutations associated with cancer in the Ashkenazi population. “The same thing occurs with everyone on the planet. It’s just harder to find,” says Isaacs. The HapMap Project, an international endeavor to describe the common patterns of human genetic variations, was beginning and their work had the potential to shed new light on the problem. It did. “In six years, we went from having no genetic risk factors for prostate cancer to as many as 70,” says Isaacs. “For the first time we could determine increased genetic risk, but the effect was small, increasing risk by 10 to 20 percent, so there really was no clinical implication,” says Isaacs.

At Johns Hopkins, with the mission of using science to improve patient care, the findings were disappointing for an additional reason. “It didn’t tell us what type of prostate cancer men were at risk for or if it should be treated,” says Isaacs. “Again, we were running into the same wall.”

“Here’s the dilemma. We know statistically that most prostate cancers are not going to progress to a point where quality of life is affected. Most men will be fine, so we say we are overdiagnosing and overtreating men,” says Isaacs. “But, prostate cancer is the second leading cause of cancer death in men. We’re not overdiagnosing and overtreating these men. To the contrary, I’d say these men are underdiagnosed and undertreated.”

So, in the United States, we have erred toward caution, Isaacs says, because we have not yet been able to unearth the genetic factors that will definitively separate the slow growing cancers from the aggressive ones. In some countries in Europe, the opposite approach is taken and prostate cancer is rarely treated because of the financial burden it would place on its socialized medical system.

“Prostate cancer is tailor-made for personalized medicine, but we need to figure out what predicts aggressive disease,” says Isaacs.

In the meantime, Isaacs heads an international consortium for prostate cancer genetics funded by the National Cancer Institute. Investigators at the University of Michigan, one of the participant groups, were getting a reproducible hits in their researched that pointed them to a region on chromosome 17. An examination of this region in the prostate cancer families collected at Hopkins revealed the same but weaker signal. Some of the most interesting genes in this region were members of the HOX gene family. The earliest information on these genes evolved from fruit fly studies.

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Isaacs recalls a prominent journal that had displayed a photo of a fruit fly on its cover. The fly had legs coming out of its head where its antennae should be due to a HOX mutation. “The legs were perfectly normal, except they were growing in the wrong place,” says Isaacs. Kimmel Cancer Center breast cancer researcher and Barbara Rubenstein Professor of Oncology Saraswati Sukumar was an expert on HOX proteins and had associated them with breast cancer development and resistance to chemotherapy. “We knew from previous work that specific HOX genes were very important in normal prostate development in mice. What if it was somehow linked to the growth of prostate cells in humans,” he wondered. Isaacs was interested in a particular gene in the HOX family, HOXB13. In mice, this gene is turned on just at the time the prostate is developing.

Working with the University of Michigan group, Isaacs focused his research on families with alterations on chromosome 17. One of these families had nine members with prostate cancer, and he had DNA from seven of them. The University of Michigan team had three families where all of the members with prostate cancer had the same HOXB13 mutation. Isaacs had to make sure it wasn’t simply a result of the mutation being common in the population, so he started genotyping everyone he could find, regardless of family history, and including men without prostate cancer. He looked at 5,000 samples and found the mutation was extremely rare in the general population, but in the men who had it, it translated to a ten times greater risk of developing prostate cancer. Finally, they also had the significant link to early onset that Barton Childs had pointed to many years earlier. The mutation was most prevalent among men diagnosed early, under age 55, and many of them had a father or brother who had prostate cancer. Now he had met both of Child’s requirements: early onset of disease and family history; and he had zeroed in on the cause. The mutation was rare in men diagnosed over age 65 with no family history.

It was a textbook case. On one hand, Isaacs was incredibly excited, on the other, he was not finding the indisputable link to aggressive disease he had hoped for, or, for that matter, one that conclusively pointed to an indolent form of the disease. “Right now, it doesn’t help us with that critical question of who to treat and who not to treat, but we feel like we’re on the right track,” says Isaacs.

The mutation was most prevalent in families of European descent. Isaacs found a different HOXB13 mutation in men of African descent, and another team of investigators found yet another mutation in Han Chinese men. “It appears there are different founder mutations for different ethnicities,” says Isaacs. It could be useful for families where a member had an aggressive prostate cancer associated with the mutation. “We could potentially test the other men in the family to see if they have mutation so that those who carried it could be monitored more closely and at an earlier time,” says Isaacs.

He continues to delve deeper into the causes of prostate cancer in African-American men where incidence and death rates are double those of white men. “Treatment is effective, and so we have to figure out how to get to these men when it will work,” says Isaacs. There are some men, he suspects who could benefit from much earlier PSA screening, perhaps starting as young as 25 or 30. Prostate cancer clinician-scientist Michael Carducci agrees. “Research finds that it is the 50-year-old guy who is more likely now to present with metastatic disease than the guy who is 65 or 75,” says Carducci. “Maybe there should be an early check to find these guys. We’re trying to figure that out, so together, our research group is evaluating limited but early screening for men at highest risk.”

In the end, Isaacs says, “It’s a mixed bag. I’m very excited about this discovery, but I also realize that this is a tough cancer to figure out, and there is still much work to be done. The good news, Isaacs says, is that at Johns Hopkins, the experts have known this, so we’re ahead of the curve. The prognostic question—which cancers will progress and kill and which ones will not—is the single most important question in prostate cancer.”

UNPRECEDENTED STRIDES
The last few years have seen unprecedented strides in drug discovery for prostate cancer. Six new drugs have been approved and prostate cancer clinician Mario Eisenberger, the R. Dale Hughes Professor of Oncology, is working with fellow clinical investigators Michael
Thapsia garganica is a 3-foot tall weed that grows wild and abundantly in the Mediterranean. It is abundant because of its not so favorable reputation. Ancient Greek writings refer to it as the “plant of death” and Arabs named the weed the “death carrot” when they witnessed that camels who ate it quickly died. In the late 1970s, a Danish chemist isolated its toxin, calling it thapsigargin. Kimmel Cancer Center researcher John Isaacs began collaborating with the chemist in hopes of harnessing its killing power to treat prostate cancer.

Thapsigargin, Isaacs found, indeed killed prostate cancer cells, but unfortunately it also killed heart cells and brain cells. “We gave it to mice, and they were dead within minutes,” he recalls. Undeterred, Isaacs, one of the world’s leading experts in apoptosis (cell death through the natural cell life cycle) began putting his extensive understanding of how cells die to formulate a version of the toxin that would be lethal only to cancer cells. He recruited the help of fellow prostate cancer researcher and clinician Samuel Denmeade, and for more than a decade the two worked to chemically modify the toxic weed to specifically and safely target prostate cancer cells.

Thapsigargin kills by making cells think they need calcium when they do not. Denmeade explains. As a result, cells are flooded with unending amounts of calcium and die. The trick was to re-engineer the lethal toxin to deliver its killing power only to prostate cancer cells. For this, Denmeade and Isaacs created a compound that remains inactive until it comes in contact with cells that secrete a protein known as the prostate-specific membrane antigen (PSMA). This modification meant that the toxin would now selectively target the prostate and, unlike its predecessor, would leave heart cells, brain cells, and other normal cells alone. In laboratory studies that used human prostate tumors transplanted into mice, their engineered drug looked promising. A three-day course of the drug shrunk tumors in half and outperformed other standard cancer drugs.

With critical funding from David H. Koch, investigators Isaacs and Denmeade worked with Michael Carducci, Angelo De Marzo, and other Kimmel Cancer Center prostate cancer experts and colleagues to take their discovery to patients. Denmeade likened their chemically modified form of thapsigargin to a medicinal grenade. When the drug comes in contact with PSMA-secreting cells, it pulls the pin, killing all prostate cancer cells in its vicinity.

Delivered by injection, the drug, now called G202, works by blocking the function of an essential protein that keeps calcium levels in cells at the correct level. In essence, it causes tumor cells to overdose on calcium and die. It also shuts down the blood vessels that feed prostate tumors.

Contrary to its namesake, the research team says PSMA is not only found in the prostate but also in blood vessels in brain, kidney, bladder, breast, colon, and lung cancers, so it has the potential to work against many different types of cancer. Laboratory findings in breast, kidney, and bladder cancers reported by the team in Science Translational Medicine support this theory.

To date, the Johns Hopkins team, and collaborators from the University of Wisconsin and the University of Texas-San Antonio, has treated 29 patients with advanced cancer in a clinical trial assessing the safety of the drug. New trials will evaluate the safety and the effectiveness of G202 in patients with prostate and liver cancers.

“What we like best about this drug,” says Isaacs, “is that it causes the cancer cell itself to bring about its own demise.”

Editor’s Note: This research was funded by the Department of Defense Prostate Cancer Research Program, the Prostate Cancer Foundation, David Koch, the Danish Cancer Society, the Danish Research Council, the Aarhus University Research Foundation, and the National Institute of Health’s National Cancer Institute SPORE(CA058236 and CA006973).
Carducci, Sam Denmeade, Emmanuel Antonarakis, and others to determine how to best integrate them into clinical practice. “We have to figure out who should get which drug or combination of drugs,” says Carducci.

Carducci says the drug discovery pipeline at the Kimmel Cancer Center has played a key role in advancing the treatment of prostate cancer. Drugs like Tasquinimod, an interesting new agent that appears to work both through the immune system and by cutting off the blood and nourishment that tumors need to grow and spread, are finding much success.

Eisenberger believes a $1.5 million gift from Jones Day, a Washington, D.C.-based law firm, will strengthen these advances by supporting work to identify molecular signatures that allow for personalized therapies and improve quality of life for men with prostate cancer. It will fund several projects, including a tissue bank, laboratory and clinical collaborations aimed at rapidly identifying new targeted immune and drug therapies, and the identification of new biomarkers for monitoring disease progression and treatment effectiveness. Eisenberger and team are exploring various novel approaches, including natural compounds that could prevent or keep prostate cancer in check, targeted hormone therapies, and immune approaches that sensitize prostate cancer cells to drug treatment.

The gift will also help support the work of laboratory scientists, including Srinivasan Yegnasubramanian who is working to identify biologic markers of response to treatment. “We want to understand why two men with metastatic prostate cancer and similar clinical features and tumor pathology can have drastically different responses to the same therapy,” says Eisenberger. They are studying tumor samples from 60 patients whose cancer spread to the bones and other sites and were then treated with androgen deprivation therapy, a type of therapy that suppresses androgen, a hormone that is known to fuel the growth and spread of prostate cancer. “If we can uncover molecular genetic clues that predict which cancers are predestined to be sensitive to treatment, we may be able to personalize treatments,” he says. “Conversely, we can use genetic biomarkers to identify men who will not respond to hormone therapy and design better treatments for this group.”

“The generous contribution from Jones Day allows us to take on these projects,” says Eisenberger. “As a result, we expect to improve and prolong the lives of men with prostate cancer.”

THERANOSTICS AND MORE

In a new approach dubbed “theranostics” because it combines the diagnostic properties of molecular imaging with cancer therapy, a multidisciplinary team of experts, including Radiation Oncology Director Ted DeWeese, and cancer imaging experts Martin Pomper and Zaver Bhujwalla, developed an idea that takes advantage of important molecular components of cancer and allows researchers and clinicians to see inside the cancer cell and view them as they are being treated.

The team is developing ultra-tiny structures called nanoparticles filled with an anticancer drug that also sensitizes cancer cells to radiation and a radiopharmaceutical or cell-imaging agent. The nanoparticle is targeted to PMSA, a biomarker for prostate cancer, so that it zeroes in on and delivers its anticancer payload specifically to prostate tumors. The particle is labeled with a radioactive isotope, which can be imaged or used to treat cancer. It is given intravenously so that it can attack cells growing anywhere in the body.

In other work, DeWeese and prostate cancer researcher Shawn Lupold became the first to show that targeted small inhibitory RNA (siRNA) could be used for prostate cancer therapy. This breakthrough research focuses on siRNA, small molecules that have the ability to interfere with the expression of genes. DeWeese and Lupold used aptamers, a guidance system of sorts, to get
the RNA molecule to its target inside of cancer cells where it shuts down cancer cells’ ability to repair the injury that radiation inflicts and, as a result, they die. The aptamers, which allow the repair-blocking inhibitory molecules to be targeted specifically to cancer cells, are unique to Johns Hopkins and considered the gold standard. Moreover, it is a platform technology that can be used not only for prostate cancer but any cancer type, simply by changing the aptamer.

Yet another nanotech approach DeWeese is exploring for prostate cancer treatment uses alpha particles, a type of radium isotope, that are naturally targeted to the bone where prostate cancer most often spreads. It captures the killing power of decaying radium, but in this form it has a short life of about ten days and only causes damage in the limited path it travels in the body. Radium has a chemical relationship to calcium, and so acts in the human body like calcium, naturally traveling to the bone.

Investigators are studying a combined nanoparticle/alpha particle/radiation treatment. The nanoparticle, loaded with its radiation-sensitizing anticancer drug, is given simultaneously with the bone-metastasis-targeting alpha particle to exquisitely and precisely attack prostate cancer and its spread.

**FIRST-OF-ITS-KIND TREATMENT**

A first-of-its-kind prostate cancer combined therapy will make surgery an option for more men. Clinical studies, led by Charles Drake, a cancer immunology expert and co-director of the Prostate Cancer Multidisciplinary Clinic, will include a prostate cancer vaccine. GVAX, the immune system-boosting vaccine developed more than a decade ago by Kimmel Cancer Center investigators will be given after surgery in combination with the anticancer drug cyclophosphamide and a new prostate hormone therapy drug called MDV 3100. The treatment is for men who are diagnosed with high-grade prostate cancers that are likely to recur. In the past, these men were not candidates for surgery because of the likelihood that microscopic tumor cells, invisible to surgeons, had already broken away from the tumor and destined the cancer to return. Drake, who is collaborating with medical oncologist Emmanuel Antonarakis and urologists Alan Partin and Edward Schaeffer, is excited to have a potentially curative treatment to offer these men. They hope to find out what immune cells are already present at the time of prostatectomy and figure what army of immune cells they need to cause an attack against prostate cancer cells. They believe the vaccine/drug treatment could work to mop up the microscopic cancer cells missed at surgery.

**REHAB AFTER PROSTATE CANCER TREATMENT**

The two big quality-of-life issues that men experience following prostate cancer surgery are urinary incontinence and erectile dysfunction. Urologic oncologist and prostate cancer surgeon Trinity Bivalacqua and nurse practitioner Kristen Burns are helping men through a new rehabilitation/survivorship clinic. Bivalacqua is skilled at both open and robotic prostatectomy, giving him both the unique perspective and the experience to help men recover from prostate cancer surgery. “If we’re going to work to cure everyone, we want to be sure we also try to eliminate the adverse quality of life issues,” says Brady Urological Institute Director Alan Partin. Any prostate cancer patient who receives surgery or radiation therapy is a candidate for rehabilitation.

Some men who experience problems may only need counseling while others could require a more invasive intervention to alleviate symptoms, but the team says they want patients to know that this service is part of the care we offer them. Initially, they will focus on Johns Hopkins prostate cancer patients only, but eventually they hope to expand the program to help patients across the country.

**PROSTATE CANCER LEGEND**

Urologist Patrick Walsh is perhaps the most famous and revered figure in the world of prostate cancer. For 30 years he served as director of the internationally renowned Brady Urological Institute at Johns Hopkins. He transformed prostate surgery by developing an anatomical approach to remove the cancerous prostate without causing life-changing side effects, taught the procedure to hundreds of urologists-in-training; and gathered information from patients that propelled prostate cancer research forward.

In June 2011, he performed the procedure he pioneered for the last time. It was his 4,569th prostatectomy. He remains a familiar figure at “The Brady,” and through the Patrick C. Walsh Prostate Cancer Research Fund continues to advance the understanding and care of prostate cancer.

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**TITANS OF PROSTATE CANCER**

Following the Johns Hopkins model, leaders in the Prostate Cancer Program never disconnected discovery from the patient. Keeping the two aligned, its investigators and clinicians have made more advances than any other place in the world.
Erick Lutz, Ph.D., has joined the Gastrointestinal (GI) Cancer Program as an assistant professor of oncology. Lutz is the fourth Viragh Research Scholar from the Skip Viragh Clinical Research Center in Pancreas Cancer. He will develop a human immunology laboratory program for GI cancers focused on deciphering the immune response within the tumor microenvironment. Dr. Lutz completed his fellowship under the mentorship of Elizabeth Jaffee, M.D., uncovering the basic immunologic principles that define immunotherapy-induced immune responses and developing new technologies to study immune responses within developing human tumors.

Channing J. Paller, M.D., assistant professor of oncology, will extend genitourinary cancer services to the Washington, D.C. campus of the Kimmel Cancer Center. Paller is a clinician-scientist focused on developing and evaluating new therapies for urologic malignancies, including prostate cancer. She is particularly interested in the role of natural products for prevention or treatment of prostate cancer. As a fellow, she worked with Michael Carducci, M.D., to study the benefits of pomegranate extract and muscadine grape skin extract for men with prostate cancer and earned Young Investigator Awards from the American Society of Clinical Oncology and Eastern Cooperative Oncology Group.

Deborah Schwartz, R.N., M.P.H., C.R.N.P., has joined the Kimmel Cancer Center Hematology Service as a nurse practitioner. She will support the development of critical pathways and educational programs to standardize hematology care. She is currently completing the credentialing process to perform lumbar punctures, bone marrow aspirates, and conscious sedation. Her previous experience includes caring for critically ill pediatric and adult burn patients in a level one-trauma center.
Richard Zellars, M.D., associate professor of radiation oncology, and Dina George Lansey, M.S.N, R.N, O.C.N., Research Associate and Clinical Recruitment Specialist, are heading the Kimmel Cancer Center’s initiative to increase minority accrual to clinical trials. Zellars has been appointed Assistant Director for Clinical Trial Accrual and will develop and oversee initiatives to increase accrual to therapeutic clinical trials with a special emphasis on minority accrual. He will continue his academic and clinical positions as a breast and gynecologic cancer radiation oncologist. Lansey, who has extensive experience as both an outpatient clinic nurse and clinical trials research nurse has helped direct efforts to improve clinical trials communication, continuity of care, and data management.

Overcoming cultural and institutional barriers and increasing minority participation in clinical trials is a priority of the Kimmel Cancer Center, and Zellars and Lansey have a longstanding interest in addressing racial disparities in cancer. Zellars created and co-leads CUPID (Cancer in Under-Privileged Indigent or Disadvantaged), a summer training fellowship aimed at attracting to the specialty oncology medical students who have a demonstrated interest in caring for poor and underserved minority populations.

Edward Allan Sison, M.D., has joined the Pediatric Oncology Program as an instructor in oncology and pediatrics. He is a physician-scientist focused on translational research of childhood leukemia, including the development of therapies targeting high-risk childhood leukemia.

Katherine Thornton, M.D., has returned to the Kimmel Cancer Center as the clinical director of the Sibley Medical Oncology Program. Thornton will be responsible for the start-up and continuing medical oversight of the medical oncology consultation/outpatient clinical service at Sibley, which is part of the Washington, D.C. campus of the Kimmel Cancer Center. She will also develop and promote clinical research at Sibley, including educational and training programs for fellows from Johns Hopkins, the National Cancer Institute, and Howard University.
Fifteen-year-old Jack Andraka received top honors (the Gordon E. Moore Award) and a $75,000 prize at the 2012 Intel International Science and Engineering Fair. Andraka won for his development of a new method to detect pancreatic cancer. Using an approach similar to that of diabetic test strips, the high school student created a simple dip-stick sensor to test blood or urine for the level of mesothelin, a pancreatic cancer biomarker. Andraka received guidance and laboratory space from Kimmel Cancer Center pancreas cancer researcher Anirban Maitra, M.D.

The 10th annual Avon Walk for Breast Cancer was held in Washington, D.C., and Johns Hopkins received a grant of $1.3 million grant to help the support the care of women at the Johns Hopkins Avon Breast Center of Excellence.

The St. Baldrick’s Foundation, a volunteer-driven charity dedicated to raising money for childhood cancer research, has awarded grants to Colleen Annesley, M.D., for her research on acute myeloid leukemia, and Kathy Ruble, Ph.D., for research on the long-term effects of cancer treatment and specifically ways to use physical activity to lower the risk of late health effects.

The inaugural Laura Ziskin Prize in translational cancer research was awarded to Stephen Baylin, M.D., Ph.D., to study the epigenetic mechanisms that cancer cells use to modify normal gene function. The prize will be shared with Baylin’s wife Feyruz V. Rassool, Ph.D., a breast cancer researcher at the University of Maryland School of Medicine. Ziskin, who died of breast cancer, was co-founder of Stand Up to Cancer.

Jef Boeke, Ph.D., was elected fellow to the 2012 class of the American Academy of Arts and Sciences, one of the nation’s most prestigious honorary societies and a leading center for independent policy research.

The Kimmel Cancer Center recognized Bobbie Burnett and her Caring Collection, which reached a landmark goal of more than $1.1 million in donations to cancer care and research through the production and sale of stained glass angels. Burnett was honored with a ceremonial lab coat and Governor’s citation. This year’s Caring Collection donation is supporting the research of Chris Gocke, M.D.

Barbara Biedrzycki, Ph.D., R.N., C.R.N.P., A.O.C.N.P., was elected to a three-year term as the Oncology Nursing Society’s (ONS) Director at Large. ONS is a professional organization of more than 35,000 registered nurses and healthcare professionals dedicated to quality oncology nursing and cancer care.

Michael Carducci, M.D., and Antonio Wolff, M.D., were named 2012 Washington, DC-Baltimore-Northern Virginia Super Doctors. Super Doctors is a listing of physicians from more than 40 medical specialties who have attained a high degree of peer recognition or professional achievement. The listing is published as a special supplement in leading newspapers and city and regional magazines.

Allan Chen, M.D., was appointed the new physician advisor for the Department of Oncology and will lead its Quality and Safety Program.

The Giant 8th annual Triple Winner Campaign raised more than $1.5 million for the Kimmel Cancer Center Pediatric Oncology Program. This adds to the $10 million Giant has already donated to our pediatric cancer program.

Alexandra Gubin, M.S.W., L.G.S.W., has been named patient navigator for the Kimmel Cancer Center’s new Pediatric Oncology Adolescent and Young Adult Patient Navigation Program. The program was created in conjunction with the Ulman Cancer Fund and will assist teenagers and young adults with cancer in understanding treatment options through individual and group support and by facilitating connections to financial, psychosocial and educational resources.

Elizabeth Jaffee, M.D., was honored at the 4th annual Office of Women in Science and Medicine event with the Vice Dean’s Award for the Advancement of Women. Jaffee was recognized for her groundbreaking work in science and medicine.

Richard Jones, M.D. received the Leukemia & Lymphoma Society Translational Research Program Award.
The students at the 2012 American Association of Cancer Research/American Society of Clinical Oncology Methods in Clinical Cancer Research workshop selected Judy Karp, M.D., for the Merrill J. Egorin Outstanding Mentor Award.

The National Comprehensive Cancer Network (NCCN) Foundation recognized Ronan Kelly, M.D., M.B.A., with its Young Investigator Award for research focused on assessing or improving outcomes of cancer care.

David Loeb, M.D., Ph.D., was awarded a grant from the Liddy Shriver Sarcoma Initiative to support his research of the molecular mechanisms and pharmacologic inhibition of bone sarcoma metastasis.

The Lustgarten Foundation awarded nearly $4 million in new research grants to advance the development of early detection and effective treatment options for pancreatic cancer. Johns Hopkins recipients were Ana De Jesus-Acosta, M.D., Ralph Hruban, M.D., Daniel Laheru, M.D., and Anirban Maitra, M.D.

Maura Kadan, R.N., M.S.N., O.C.N., Peggy Lang, C.R.N.P., M.S.N., Marian Raben, M.S., PA-C., provided information on cancer screening, education, clinical trials, treatment and cancer care at the 2012 B’More Healthy Expo. An estimated 20,000 people attended the convention designed to get people moving, taking action and making choices to be healthier.

Kimmel Cancer Center Director William Nelson, M.D., Ph.D., was selected to be a guest on BioCentury as part of a panel discussion to explore why collaborative boundaries need to be reinvented to translate curiosity-driven science into patient value. The program spotlights the views of key scientific opinion leaders, corporate decision makers, lawmakers and policy architects, venture capitalists and other investment professionals, and the patient and consumer groups who stand to benefit most from biotechnology.

Timothy M. Pawlik, M.D., M.P.H., head of the Johns Hopkins Liver Tumor Center, has been appointed the new director of surgical oncology at the Johns Hopkins University School of Medicine.

As part of its Hyundai Hope on Wheels program, Hyundai dealers named pediatric oncologist Eric Raabe, M.D., Ph.D., a 2012 Hyundai Scholar and presented him with a donation to support his brain cancer research.

Martin Pomper, M.D., Ph.D., and John Issacs, Ph.D., each received a Prostate Cancer Foundation Challenge Award. They were among nine recipients selected from a pool of 96 applications received from 10 countries. The awards, a $9 million investment over a two-year period, are made to accelerate scientific discovery and new treatments for prostate cancer.

Paul Reed Smith Guitars hosted the acclaimed “One Night, One Show, One Cause,” featuring Journey at the Modell Center for the Performing Arts at the Lyric Opera House. The event raised $250,000 for the Living with Cancer Resource Program at the Hopkins Kimmel Cancer Center.
lives, spent less time in the hospital, and lived three months longer. The same results were seen in other studies. These findings led the American Society of Clinical Oncology to recommend that every seriously ill cancer patient get palliative care.

Secondly, it reduced costs. Effective symptom management keeps patients out of the hospital, and as a result, there is a significant cost savings.

Managing burgeoning health care costs, whether we like it or not, is part of our reality. Insurance premiums for a family of four have risen from $7,000 to over $15,000 in the last ten years. Patients are faced with it when they consider expensive treatments with large copays, and providers of care need to think about it too. We simply cannot sustain these rising costs. When we looked at our own patients, we found that one-third had chemotherapy within two weeks of their deaths. There is more and more evidence that this is not helpful, and in fact, it could be harmful and actually shorten peoples’ lives. More money does not always translate into better care, and by the same token, spending less money does not equate to lesser care. We need to recognize when continuing chemotherapy or radiation therapy is no longer the best thing for the patient.

What caused the big shift?
There were a couple of things that happened. First and foremost, we proved that palliative care had a favorable impact on survival. Two separate studies found that patients with advanced cancer who received palliative care lived longer than patients who did not. A study of lung cancer patients showed that those who had palliative care from the onset, used less chemotherapy at the end of their treatment doesn’t work, patients can make a smooth transition to this team.

What do you have planned for the pain and palliative care program?
I would like to see Johns Hopkins where it rightfully should be, a national leader in palliative care. The Duffey family shares our vision, and we are fortunate because they have provided us ongoing funding to make this happen. We plan to add doctors and advanced practice nurses to our team. Currently, we have outpatient and inpatient palliative care consultations. By 2013, we hope also to have an inpatient unit.

We have already established a palliative care research fellowship and have received two research grants. We would like to add a clinical fellowship. We are establishing and expanding interdisciplinary relationships with the School of Public Health and the School of Nursing to ensure we are truly providing the best and most advanced care possible in keeping with the Johns Hopkins tradition.

MEET TOM SMITH
THE BENEFITS OF PALLIATIVE CARE

THOMAS J. SMITH, M.D., is one of the world’s leading experts in palliative care and an accomplished cancer clinician and researcher. He recently joined the faculty of the Kimmel Cancer Center as the Harry J. Duffey Family Professor of Palliative Medicine and Director of Palliative Medicine at Johns Hopkins. Smith shared his thoughts on the evolution of palliative care and his goals for the Kimmel Cancer Center.

What is palliative care?
I usually tell people that it is hard to define, but you know it when you see it. In literal terms, it means the management of symptoms—controlling pain, shortness of breath, depression, anxiety and those things that affect patients’ quality of life. The greatest misperception is that palliative care is only end-of-life care. In fact, it is survivorship care. We now know that palliative care is beneficial for all patients with advanced cancer from the time of diagnosis, not just at the end of life.

Palliative care was introduced as a medical specialty in 1990, but just a handful of hospitals offered it. Today, 90 percent have some type of palliative care program or service.

What caused the big shift?
There were a couple of things that happened. First and foremost, we proved that palliative care had a favorable impact on survival. Two separate studies found that patients with advanced cancer who received palliative care lived longer than patients who did not. A study of lung cancer patients showed that those who had palliative care from the onset, used less chemotherapy at the end of their
IN THE NEWS

HONORS AND AWARDS

Safeway funded pilot breast cancer research grants to Leisha Emens M.D., Ph.D., Edward Gabrielson, M.D., Josh Lauring M.D., Ph.D., Saraswati Sukumar, Ph.D., Antonio Wolff, M.D., Luigi Marchionni, M.D., Ph.D., and Linda Resar, M.D. Also, in honor of Safeway’s annual campaign to support prostate cancer research, Kimmel Cancer Center Director William Nelson, M.D., Ph.D., and Prostate Cancer Program Co-Director Michael Carducci, M.D., served as guest grocery baggers at one of the store’s Baltimore City locations.

Cynthia Sears, M.D., and Peter Searson, Ph.D., are among the first recipients of grants geared to answer “Provocative Questions” in cancer research, a new project funded by the National Cancer Institute. Grants are aimed at providing answers to one of 24 questions, solicited from the research community, that address neglected or unsolved areas of cancer research. Sears will explore how and why certain cancers may be caused by infections, and Searson will develop a new method to study how cancer spreads.

C. Michael Armstrong Professor Gregg Semenza, M.D., Ph.D., was recognized for outstanding professional achievement and commitment to service with his election into the Institute of Medicine, one of the highest honors in the fields of health and medicine.

The Tigerlily Foundation presented Lillie Shockney R.N., B.S., M.A.S., with its Inspiration Award. The foundation mission is to educate, advocate, empower and provide support to young women with breast cancer.

Donald Small, M.D., Ph.D., received the Alex’s Lemonade Stand Foundation Innovation Award to support his research of novel treatment for pediatric cancers.

The Tenfold Forty, an organization of 40 professional women honored Connie Trimble, M.D., for her clinical research in the treatment of HPV-related cervical cancer with a check to benefit the Cervical Dysplasia Center at the Kimmel Cancer Center.

World renowned urologist Patrick C. Walsh, M.D., who pioneered work in the understanding and treatment of prostate cancer, was honored with the American Academy of Arts and Sciences’ prestigious Francis Amory Prize on March 14. Given by the Academy since 1940, the prize recognizes major advances in reproductive biology and medical care.

Bert Vogelstein, M.D., was awarded the American Association of Cancer Research (AACR) Eighth Annual AACR-Irving Weinstein Foundation Distinguished Lectureship. This Lectureship was established in 2004 to acknowledge an individual whose outstanding innovations in science and whose position as a thought leader have the potential to inspire creative thinking and new directions in cancer research.

The Oncology Nursing Society (ONS) has awarded Jennifer Wenzel, Ph.D., R.N., C.C.M., the 2012 Excellence in Writing Award for Qualitative Nursing Research.

Christopher L. Wolfgang, M.D., Ph.D., was selected to lead the hepatobiliary and pancreas surgery unit, one of two newly created sections within the Department of Surgery. Nita Ahuja, M.D., heads the gastrointestinal oncology, breast, melanoma, sarcoma, and endocrine section.

YOU’RE BEAUTIFUL
Patients and staff in the Division of Pediatric Oncology created a YouTube sensation with their video “You’re Beautiful.” Patients, families and staff lip sync to the popular British boy band One Direction’s song “What Makes You Beautiful.” One Direction band member Liam Payne is one of the fans. He tweeted about the video.

ABINGTON HEIGHTS HIGH SCHOOL SCORES WITH RED CARD CANCER
Abington Heights High School Boys Soccer Team in Clarks Summit, Pennsylvania continued their support of Red Card Cancer raising $4,000 for the cause. Under the coaching of Steve Klingman, Abington Heights High School has separated themselves in supporting Red Card Cancer and carrying the message to the community that, “Together We Can Make a Difference.”

ON THE WEB

WWW.HOPSKINSKIMMELCANCERCENTER.ORG
COMMONWEALTH CANCER SUMMIT

THE COMMONWEALTH FOUNDATION for Cancer Research, under the direction of Board Chairman William Goodwin, has been a leading supporter of translational, bench-to-bedside research at the Kimmel Cancer Center. After a review of research being conducted at cancer centers throughout the country, Goodwin and the Commonwealth Foundation identified the Kimmel Cancer Center and the Memorial Sloan Kettering Cancer Center as hotbeds of meaningful research that could be quickly applied to patient care. Investigators from both centers came together last summer for a cancer summit to discuss opportunities for collaboration.

Promising personalized cancer detection and treatment approaches inspired by Commonwealth funding include new tests for cancer and vaccines and other cancer-fighting immune strategies.

CLINICAL BIOMARKER TESTS FOR CANCER

The Kimmel Cancer Center has become an incredible engine for biomarker discovery and for developing tests and platforms to evaluate and assess their benefit. Central to this is a new clinical sequencing laboratory focused on translating genetic and epigenetic research and findings into clinical tests that will guide cancer diagnosis, risk stratification, and therapy. Clinical experts, laboratory medicine experts, and genomics experts are working together to figure out how to move this science and technology forward.

Investigators believe that extremes in patient responses to the same therapy could be rooted in alterations in the cancer genome and epigenome. Using sequencing technology to compare the genetic and epigenetic characteristics of cancers that responded well to a treatment to those that did not, could reveal important new predictive biomarkers to differentiate patients who are likely to respond to a particular treatment from those patients who will not. The collaborative team of clinicians and investigators will apply the technology and method to two cancer types per year to develop an individualized treatment approach that can be studied and validated in large, multi-institutional studies.

The team has already begun studies of prostate cancer, ovarian cancer, and pancreas cancer to identify the changes that cause treatment resistance specific to each cancer as well as those that translate to better outcomes. The researchers believe that if they can decipher the molecular characteristics that make a seemingly aggressive and lethal cancer have a long-lasting response to treatment, they can potentially use drug interventions to convert less responsive tumors and make them more amenable to treatment. These biomarkers could then be used to guide personalized cancer medicine, getting the right treatments to the right patients.

PROVOKING AN IMMUNE RESPONSE TO CANCER

Kimmel Cancer Center cancer immunology experts have had breakthrough discoveries related to an immune inhibitory checkpoint called PD-1. It is co-opted by tumors to shut down an immune response to cancer cells. Two clinical trials that used antibodies to block PD-1 and PD-L1, a related molecule that binds to PD-1,
resulted in significant and long-lasting responses against melanoma skin cancer, renal cell (kidney) cancer, and lung cancer. The findings in lung cancer were particularly significant as it was not thought to be an immune-responsive cancer. Experts say it demonstrates that, with the correct approach, essentially all cancers could be made vulnerable to immune attacks.

This research adds to the growing body of evidence that the immune system is not passively tolerant to cancer but that cancer cells actively hijack immune pathways to acquire immune resistance. A tumor recognizing it is under attack by immune cells, up regulates PD-L1 to shut down the immune response. Conversely, in their studies tumors that did not engage PD-L1 did not respond to treatment. The finding opens the door to using PD-L1 as a predictive biomarker for identifying patients who will respond to anti-PD-1 therapies, but also as a target for combined treatments in patients whose tumors do not express PD-L1.

Vaccines or other immune-targeted approaches could potentially be used to activate PD-L1 and prime them for subsequent anti-PD-1 treatment. The lung cancer studies, revealed potential synergy with epigenetic-targeted treatments and anti-PD-1 therapy.

The anti-PD-1 success has revealed a need for better ways to monitor these cancers. PD-1 targeted cancers are characterized by progression before regressing. Imaging scans, such as CT, for this type of therapy do not tell investigators what they need to know. Researchers are exploring the possibility of tests that measure tumor DNA in the blood to quantitatively analyze if the treatment is working.

These findings have inspired new collaborations funded by the Commonwealth Foundation and Stand Up to Cancer. Investigators believe that PD-1 is just the tip of the iceberg and that there are 10 to 15 additional immune checkpoints that are coordinately and differentially expressed in tumors. They are all potentially targetable with antibodies, molecular profiles of the tumors could be used to reveal these checkpoints and guide treatment.

**NOVEL METHODS OF CANCER DETECTION**

The research team that deciphered the genetic blueprints for cancer is using their findings to develop clinical tests performed on routinely collected biological fluids, including plasma, sputum, stool, and urine, to detect cancers in an early and curable stage and to monitor the effectiveness of targeted treatments in existing cancers. The tests in development are specific to cancer, have a low rate of false positives, are cost effective, and high throughput so they can rapidly process large quantities of DNA and information and be used routinely. The investigators envision such tests, which identify the unique genetic and epigenetic changes that define cancer, becoming part of a person’s regular physical.

These changes are almost always present in early cancers, but the challenge is advancing the sensitivity of the tests to detect a minute amount of cancer DNA circulating within a sea of normal cells. Almost all of these changes are present before a cancer spreads, and they are not simply associated with cancer, as PSA (Prostate Specific Antigen) and other markers currently used for cancer detection, they are the cause and driver of cancer growth and progression. The greatest success has been achieved in tests for colon cancer and ovarian cancer. Other cancers, such as brain cancers, are proving more difficult. The research team is working with cancer clinicians to determine the best medium—i.e., plasma, stool, etc.—best suited to the detection of each specific cancer. Once the tests are perfected they can be used to monitor people at increased risk of developing cancer.

**PERSONALIZED CELL THERAPY**

Bone marrow transplant and blood and bone marrow cancer experts have developed a personalized treatment approach that uses patients’ own immune cells to fight their cancer. It focuses on a type of tumor-specific T-cell. For cancers of the blood, these cells, known as marrow infiltrating lymphocytes or MILs, are found in the bone marrow where the cancer originates.

In their normal capacity, the cells are inactive and somewhat small in number so they have little effect against the cancer, but our experts are using a clinical concept known as adoptive T-cell therapy, in which they retrieve a patient’s own MILs from his or her bone marrow, grow the cells in a specialized laboratory to expand their numbers and then return them to the patient where they seek out and destroy cancer cells. The Kimmel Cancer is one of a few cancer centers in the U.S. that perform adoptive T-cell therapy, and, it is the only one using MILs. Currently, the therapy is being studied in multiple myeloma, an incurable cancer of the blood plasma cells, but research indicates that this personalized cell therapy would be beneficial in treating a variety of blood and bone marrow cancers and likely solid tumors as well. Cell therapy is also being explored in other medical disciplines, including cardiology.

In multiple myeloma, MILs cell therapy is used in conjunction with bone marrow transplant to prime antitumor immune response and improve the effectiveness of the transplant. Our experts believe this therapy will improve the duration of responses and may one day replace the need for any additional treatment.

**PERSONALIZED PANCREAS CANCER VACCINES**

Cancer immunology experts continue to optimize the effects of the pioneering pancreas cancer vaccine they developed more than a decade ago. New work includes the use of peptides to individualize vaccines to the unique molecular characteristics of each patient’s cancer and, as a result, improve their response against pancreas cancer.

Peptides are the building blocks of proteins and are a “table of contents” of sorts displayed on the cell surface to reflect the internal molecular structure of the cell. Vaccines could use peptides to prime immune cells to recognize when something is not right within a cell, as in cancer. Researchers are studying whether identifying peptides that mark each patient’s specific tumor cells and incorporating them in the pancreas cancer vaccine could boost the immune response against cancer cells.

Other work includes use of multiple vaccinations to maintain long-term immune activity against tumor cells.

The team’s ultimate goal is to combine cancer vaccines that target the individual genetic alterations within the patient’s cancer cell with immune modulating agents that maximize the immune response against the cancer.
PHILANTHROPY

PREVENTING BREAST CANCER
THE JOHN FETTING FUND FOR BREAST CANCER PREVENTION

“Our goal should be to do more than cure breast cancer. We must prevent it,” John Fetting told a group of people who came to the Kimmel Cancer Center to learn about the Fetting Fund for Breast Cancer Prevention. Fetting, a breast cancer clinician for more than three decades believes that recent research breakthroughs about the biology of breast cancer can now be applied to prevent it from occurring at all.

“Over the course of my career, I’ve seen substantial progress made against breast cancer, and I’m very gratified by that,” says Fetting. “Screening mammography has led to earlier diagnosis, and treatments have become more effective, so more patients are surviving and living full lives. Still, I think we can do better. With the same kind of concerted effort that has been mounted to cure breast cancer, we can prevent it from ever occurring.”

After battling breast cancer herself, Leslie Ries became a proponent of prevention. “Advances in treatment options are not enough. We have to try to protect ourselves, our children, and others from getting this disease,” says Ries who helped to establish the Fetting Fund with her husband Tom to allow laboratory discoveries to be translated into prevention strategies. To date, with a lead gift added by Lorraine and Mark Schapiro, $1 million has been raised toward the cause. Fetting treated the Schapiros’ daughter. “He was fabulous, but I wish we never had to go through this,” says Mrs. Schapiro. “Prevention is better than a cure, and we need to start moving in that direction.”

Fetting says that discoveries made at the Kimmel Cancer Center that reveal the genetic (mutations to DNA) and epigenetic (nonmutational alterations to DNA) changes that cause breast cancer can be used to better distinguish those women at risk for breast cancer so that clinicians can intervene early before the cancer can cause her harm. “One in nine women will be diagnosed with breast cancer,” says Fetting. “That means one will get breast cancer but eight will not. We need to advance our science so that we can identify ‘the one’ and intervene to prevent breast cancer. We also need to use this science to identify and reassure the eight who will not,” he says. “A normal cell does not become a breast cancer overnight,” says Fetting. “It happens over many years, so we can look for this genetic and epigenetic signature of breast cancer and figure out who has these changes and who does not.”

Kimmel Cancer Center breast cancer experts are examining several ways to interfere with the biological changes that set breast cancer in motion. Breast cancer experts are investigating the protective effects of certain natural chemicals found in fruits and vegetables and figuring out how best to deliver them to individuals. They also are studying ways to halt the molecular and cellular changes that trigger breast cancer with drugs that reactivate key tumor suppressor genes that had been turned off through epigenetic alterations.

Leading cancer experts agree that prevention is one of the best ways to manage cancer risk, however, it is an area of cancer research that is currently underfunded. “The Fetting Fund will support this type of work so that we can begin to replace fear with hope,” says Ries, “because we all deserve a future without breast cancer.”

For more information on the Fetting Fund for Breast Cancer Prevention or to make a contribution, contact Dina Klicos at 410-516-4203 or cklicos1@jhmi.edu

SWIM ACROSS AMERICA

SWIM ACROSS AMERICA

MAKING WAVES TO FIGHT CANCER
Over the last three years, the Swim Across America (SAA) Baltimore event has raised more than $1 million for the Kimmel Cancer Center creating the Swim Across America Laboratory at Johns Hopkins directed by gastrointestinal cancer physician-scientist Luis Diaz, M.D. The money is helping Diaz and his team develop gene-based tests that can detect cancer, monitor its progression, and pinpoint the best treatments. “We have made a lot of progress with the Swim Across America donations. We are applying it to research against cancers that are hard to treat and where there are currently no standard therapies that are curative,” says Diaz. “This support makes it possible for us to take the best ideas and bring them to patients.”

Swim Across America funds also support a number of patient-directed initiatives including new clinical trials for targeting pancreatic cancer and advanced colon cancer; a survivorship clinic for colon cancer patients who have finished treatment; and a special three-day couples retreat for colon cancer patients with advanced disease and their caregivers.

Hundreds of swimmers took to the water at Meadowbrook Aquatic Center in Baltimore and the Waltjen-Shedlick Farm near Gibson Island on September 23 for the 2012 event. As in the previous two years, a number of current and former Olympic swimmers joined the pool and open water events including Brad Snyder and Ian Silverman (both gold medalists at the 2012 London Paralympics), Craig Beardsley, Brenda Bartlett, Wendy Weil and Tara Kirk Sell. During their time in Baltimore they also stopped by the Kimmel Cancer Center to visit children with cancer and their families.

This year’s event also included a special tribute to Alec Cosgarea. Seventeen-year-old Alec was a world-class swimmer and Swim Across America veteran who organized “angel swimmers” matching accomplished swimmers like himself with novice participants as companions for the open water swim. Tragically, Alec was killed just months before the event in an automobile accident, but his spirit was an unmistakable and powerful part of the day’s event. Many thousands of dollars were
that target specific gene alterations within a patient’s cancer. Clinicians decide which drugs will work against the cancer based on the alterations they find inside the cells’ DNA.

Cancer is generally characterized by a combination of tumor cell-suppressing genes being turned off and growth-promoting oncogenes getting turned on. Each person’s cancer has a unique combination of these molecular mistakes contained within the sequestered DNA of the cancer cell. This genetic fingerprint helps determine which drugs are likely to work against the cancer and which ones will not.

When a treatment does not work, resistance mutations are often the cause. A cancer cell is, after all, a normal cell that has errantly acquired genetic traits that allow it to grow immortally and uncontrollably. Resistance mutations occur among these alterations and they add up over time as cancer cells divide and grow. “Tumors always contain thousands of resistance cells,” says Luis Diaz, director of the Kimmel Cancer Center Swim Across America Laboratory. The more advanced a cancer is, the more resistance alterations it acquires, giving the cells that contain them a greater chance to survive treatment.

Diaz worked with leading cancer genetics researchers Bert Vogelstein and Kenneth Kinzler, co-directors of the Ludwig Center for Cancer Genetics and Therapeutics, to better decipher and understand the molecular origins of targeted therapy resistance.

The team analyzed blood samples from 28 patients with advanced colorectal cancer who were being treated with a drug that targets an important tumor cell growth pathway known as EGFR. Patients most likely to respond to the targeted agent have normal copies of the cell-growth-promoting oncogene known as KRAS. Among the study group, only four patients tested positive for mutations of the KRAS gene. Researchers would not expect them to respond to the treatment, but the remaining 24 should have benefited. So why have so many of these patients relapsed? The answer, Diaz, Vogelstein, and Kinzler found, was there all along. The resistance mutations were already there. They were simply undetectable until the tumor grew.

As cancer cells multiply, they shed DNA into the blood and reveal the genetic mutations contained in the cell. The more cancer cells there are, the more DNA that is shed. Diaz, Vogelstein, and Kinzler have lead the world in developing blood and other tests that pluck this obscured DNA from within a sea of normal cells. They used this technology to periodically look for cancer DNA in simple blood samples obtained from the patients. Five to seven months into treatment, their test revealed that nine of the patients who began treatment with normal KRAS genes, now had KRAS mutations. This molecular evidence foretold that the cancers would continue to grow even before the advancing disease could be detected in imaging scans, but when did these mutations occur?

The team called upon the mathematical expertise of Harvard University colleague Martin Nowak who developed a mathematical model to date these alterations. He found that KRAS mutations were present, just undetectable, before the patients even began their targeted treatment. Although the studies were in colon

AN EXAMPLE OF WHERE SAA MONEY GOES

UNMASKING CANCER’S HIDDEN DEFENSES

It is perhaps the most challenging and frustrating aspect of cancer therapy, for doctors and patients alike. A treatment works; the cancer shrinks, and then suddenly the treatment is no longer effective, and the cancer returns with a vengeance. New findings from Swim Across America and Ludwig Center researchers have begun to unravel what happens within the cancer cell to cause its resistance to treatment. In fact, their research finds, the origins of the cancer treatment resistance were hidden in the cancer cell all along.

Personalized therapies involve drugs that target specific gene alterations within a patient’s cancer. Clinicians decide which drugs will work against the cancer based on the alterations they find inside the cells’ DNA.

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cancer, Vogelstein says the findings likely apply to all targeted therapies. “This means that the development of drug resistance with single-agent targeted therapies is a fait accompli,” Vogelstein concluded. “Long-term remissions of advanced cancers will be nearly impossible with single targeted agents.” It’s really just a matter of when they will recur. That, he says, simply depends on how long it takes cancer cells with the mutant genes to multiply.”

“This latest research adds to the building body of evidence that metastatic cancers will be nearly impossible to control. The ideal opportunity to cure cancer lies in detecting it early when tumors are small and have fewer resistance genes or can be removed with surgery.

Multi-drug and method combinations that simultaneously attack a variety of genetic cancer drivers or reactivate silenced tumor suppressor genes are a better option, and Vogelstein is calling for a change in how the cancer world conducts early clinical trials whose participants are almost always patients with advanced cancers. “Since we know that single agents will not have long-term success, we need to start testing new drugs as combination therapies much earlier,” he says. “There are a limited number of gene signaling pathways that go awry in cancer, so it should be possible to develop a small number of agents that can be used in a large number of patients.”

In addition, Director William Nelson, wants to begin using the Kimmel Cancer Center’s clear edge in cancer genetics discovery and application to develop screening tests that would detect cancers when they are very new and before they cause any symptoms. “We need to move away from a system in which we see patients for the first time when they begin experiencing symptoms to one that detect, manages, and eradicates cancers before people even know they have them,” says Nelson.

“Imagine, for example, if we could find cancers early enough that we could burn them off much like we do with a wart,” says Nelson. “I think this is within the realm of possibility, and I think our Center is uniquely positioned to make it happen.” He points to colonoscopy. It is a screening test that, when performed correctly, detects precancerous polyps in the colon that can be removed during the screening to prevent a colon cancer from ever occurring. “We need similar types of strategies for all cancers,” says Nelson.

Once these techniques are developed, the challenge then is not to overdetect and overtreat cancers, and this is where he again believes Kimmel Cancer Center science can inform. The same molecular genetic information that is being used to personalize cancer treatments can be used to personalize cancer screening and detection. Rather than a one-size-fits-all, Nelson says the frequency and intervals of cancer screening can be determined by looking at the cellular cues. It will point us toward abnormal cells, like polyps, but also tell us which ones need attention and which ones can be left alone. The end result, says Nelson, is that that we will not only improve cancer outcomes, but also reduce the adverse affects that come with overscreening and overtreating. He says, “We will be able to preserve health by preventing cancer, very accurately predict who will get cancer, and personalize treatments to get the right treatments to patients who need them and spare those who will not benefit.”

INNOVATIVE RESEARCH

Brian Ladle, M.D., is the 2012 Optimist Fellow at Johns Hopkins. His research focuses on immunotherapy and novel new therapies that trigger the body’s own immune system to recognize and attack cancer cells, just as they do bacteria, viruses, and other foreign invaders. Since cancer cells arise from normal cells, they most often go undetected by the immune system, but Johns Hopkins investigators have been on the cutting edge deciphering the mechanisms by which immune cells are activated, and plan to apply this new knowledge to innovative therapeutics. The immune system, much like cancer, is quite complex.

Applying immunology to cancer patients is more difficult still as their immune systems have already been compromised by the drugs used to treat cancer. Dr. Ladle will be working with other senior investigators to uncover chinks in the immune system’s armor that will allow them to turn off the defense mechanism of tumors and ramp up the immune system’s attack against them.

OPTIMIST INTERNATIONAL HELPING TO UNLOCK THE MYSTERIES OF PEDIATRIC CANCER

Optimist International has been a vital partner to Johns Hopkins Pediatric Oncology in its fight against childhood cancer. A $1 million legacy endowment has helped our clinician-scientists realize breakthrough discoveries. The success of this partnership is best reflected in the lives of the many children who have benefitted from innovative therapies developed by our Optimist Fellows. For the first time in the history of cancer medicine, the technology exists to quickly decipher the cellular causes of every cancer. Kimmel Cancer Center researchers have pioneered the science that has led us here and were the first to crack the genetic code of a pediatric cancer. What we have learned is now allowing our scientists to target the very biological mechanisms that cause a cancer to grow and spread. With these discoveries, they can begin toalter the course of pediatric cancers in ways that could only be imagined a decade ago.

Optimist International has generously made an additional commitment to make sure we get there. The Optimist International Innovative Research Fund will allow us to significantly expand our clinical and research programs in childhood leukemia, pediatric brain tumors, sarcomas and other solid tumors, and bone marrow transplantation.
COMING SOON
KIMMEL CANCER CENTER
ON THE iPad®

Look for more information on this and other news at hopkinscancer.org