

# DISCOVERY

The Brady Urological Institute • Johns Hopkins Medicine

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A PUBLICATION OF THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND



On the 11th floor of the new Sheikh Zayed Tower is our state-of-the-art Christina and Robert C. Baker Prostate Cancer Care Center, a beautiful space designed for healing.

## “We’re Not In Kansas Anymore”

### Donor’s Gift Helps Transform Brady Hospital Space

If you’ve been in Baltimore recently, you may have noticed that the skyline is a lot prettier. There is a beautiful, glittering, new \$1 billion clinical building on Orleans Street. It’s been under construction for five years, and ranks as the most expensive building project in Baltimore’s history. Patients and doctors alike agree the result was well worth it. There are two 12-story towers: One is the Charlotte R. Bloomberg Children’s Center, named for New York Mayor Michael Bloomberg’s mother, and the other is the Sheikh Zayed Tower, named for the founding president of the United Arab Emirates. The new building covers 1.6 million square feet and has 560 private rooms. There are three floors of operating suites, 33 state-of-the-art operating rooms, and radiology suites featuring the latest imaging technology.

Thanks to the commitment and generosity of Christina and Robert Baker, the Brady Urological Institute now has “truly phenomenal space, unlike any other facility we have ever had,” says Brady Director Alan W. Partin, M.D., Ph.D. The new space, on the 11th floor of the West Sheikh Zayed Tower, built with the help of a \$5 million gift from the Baker family, is called The Christina and Robert C. Baker Prostate Cancer Care Center. “From the rooms that line the hallways to the very people who bring modern medicine to the bedside, thanks to the Bakers’ remarkable gift, we have completely transformed the way we are able to care for our patients.”

To men and their families who spent time recovering from surgery in the Brady Pavilion on Marburg 2, Partin says, “To quote Dorothy in the *Wizard of Oz*, ‘We’re not in Kansas anymore.’”

With precision planning and the help of many people, the Department of Urology made the transition to the Baker Prostate Cancer Center in a single day. In a matter

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### THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND

#### FOUNDERS’ CIRCLE

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### Telling the Story



The story of discovery at the Brady is a timeline of progress and hope.

I am always so happy to write this letter, and to tell you about our wonderful progress in understanding and treating prostate cancer. What I hope you will notice, as you read about our very latest discoveries, is that many of the stories are told in context. They are links in a very long and important chain.

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For example, Karen Sfanos's exciting work connecting the chemical PhP and infection to prostate cancer wouldn't have been possible without earlier work done by Bill Nelson and Angelo De Marzo. Bill Isaacs' discovery of the most important gene so far linked to prostate cancer didn't just happen. It's based on two decades of genetics research (see the timeline on Page 4). Much of that work was arduous, time-consuming and unrewarding, because when Billy first started doing this, he didn't have the luxury of the computer programs that now allow him and his colleagues to sift much more rapidly through vast amounts of data. He and his team kept going through false leads, investigating numerous genes in families hit hard by prostate cancer over the years, looking for connections. And this genetics work, in turn, came about after observations by Patrick Walsh that prostate cancer – which everybody used to assume was just a disease that happened in older men – seemed to run in families, and that in these families, men developed it at a younger age.

We are telling the story of the discovery of prostate cancer because we have lived it. It is woven into the fabric of our laboratories, our clinics, and our operating rooms. Discovery after discovery, based on observations and teaching by the people who have been at the forefront of this disease for nearly a century. I hope you will see this issue of *Discovery* as part of a continuum, a timeline of progress and hope.

I also hope that you will be as excited as we are about our beautiful new hospital floor. I truly believe that there is nothing like it anywhere in the world. The whole space was designed, with ideas from patients, doctors and nurses, to be a place for healing. It would not have been possible without a very generous gift from Christina and Robert C. Baker, and this brings me to our amazing patients. We are so blessed that the people who come to us for treatment, who could easily be forgiven for turning inward during a difficult time, instead reach outward. On the back cover is the story of John McDonald, who has devoted his life to raising money to help other people fighting cancer. Patients giving back, helping other patients, and helping us care for them. To me, that's the best story of all.

Best wishes,

Alan W. Partin, M.D., Ph.D.

David Hall McConnell Professor and Director  
The Brady Urological Institute

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of a few hours, “we increased our capacity from 21 to 32 beds, and expanded from 5,600 to 13,600 square feet of inpatient space,” recalls Partin. The extra space means that each room is now a private room, “giving our patients and families added privacy and comfort as they recuperate.”

The whole building was designed to be a soothing place for healing. In keeping with that, the Baker Center has new pager systems, rubberized floors and acoustic ceiling tiles designed to reduce noise levels. Nurses' workstations are located between every two patient rooms, to help them stay closer to the bedside.

The Bakers' gift adds to a tradition of philanthropy that dates to the very beginning of the Brady Urological Institute. “The creation of the building that housed the Brady Urological

Institute from its founding days was made possible by a philanthropic gift from James Buchanan “Diamond Jim” Brady in 1912,” notes Partin. “His foresight and generosity transformed the way urology was practiced and paved the way for a century of medical discovery, superb patient care, and unsurpassed training opportunities for young urologists.

“One hundred years later, the Bakers and many other patients and friends of Johns Hopkins Urology have demonstrated that same kind of foresight and generosity time and time again, through their own personal philanthropic investments in the Brady. We couldn't be more grateful. Christina and Robert Baker's decision to make a gift to make our new patient care floor possible is already making a difference to this Institute, its patients, and our medical providers, and will continue to do so for decades to come.”



## Spotlight on Giving

Christina and Robert C. Baker are Founding Members of the Johns Hopkins Prostate Cancer Advisory Board. Mr. Baker, a member of Johns Hopkins Medicine's Board of Trustees, serves on the Board's Facilities and Real Estate Development Committee, which was instrumental in the construction of the new Sheikh Zayed Tower. Robert Baker is the Chief Executive

Officer of the National Development Realty Corporation, one of the nation's leading real estate development and management firms, with over 22 million square feet of office space across 14 states. Mrs. Baker is an expert equestrian who enjoys the competition of dressage.

*Richard Baker, Lisa Baker, Serena Baker, Jack Baker, Mrs. Christina Baker, Mr. Robert Baker, Ashley Baker, Dr. Alan W. Partin*

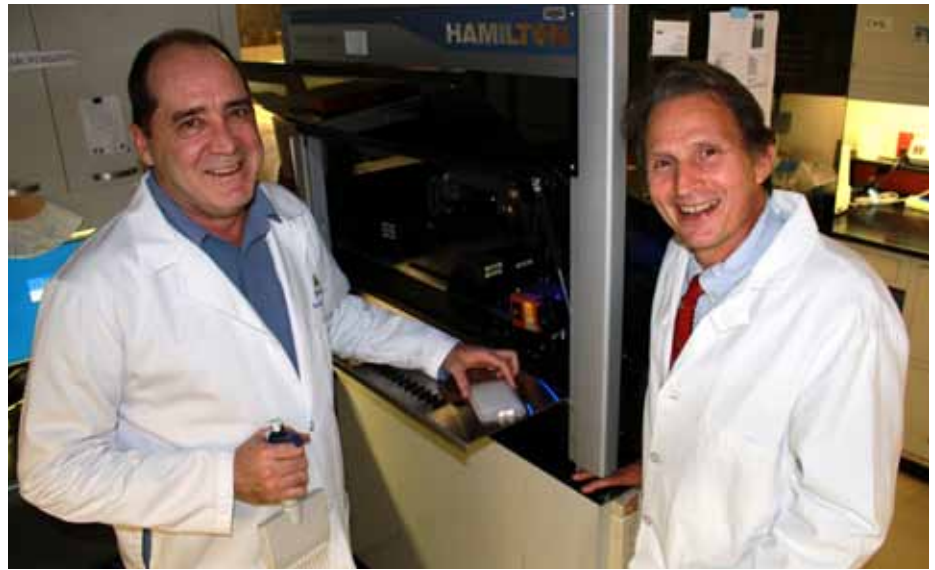


## Hereditary Prostate Cancer Risk: A Major Gene Mutation Is Found

Bill Isaacs might not have imagined it would take more than 20 years, but he knew he was in for a long, tough haul when he started searching for genetic links to cancer in families that had been devastated by prostate cancer. With the technology that existed in the late 1980s, it was a nightmare version of “find the needle in the haystack” – with millions of potential needles in hundreds, and then thousands, of haystacks. But Isaacs, Ph.D., his dedicated research team and soon, collaborators at other institutions, plugged away. It made sense that a major mutation had to be out there: Something was clearly different with these families, most of whose men tended to develop prostate cancer, and at a younger age. But for a very long time, the genetic Holy Grail of a “highly penetrant” gene – a mutation that, if inherited, will dramatically raise a man’s risk of developing prostate cancer – proved elusive.

Not anymore. In exciting work published in the *New England Journal of Medicine* early in 2012, Isaacs and colleagues at Johns Hopkins and the University of Michigan Health system reported finding what appears to be the *first major gene mutation associated with a high risk of the disease* in hereditary prostate cancer families. This research was made possible in large part through the generous support of Mr. P. Kevin Jaffe. Men who inherit this mutation are 10 to 20 times more likely to get prostate cancer than other men. (Hereditary prostate cancer was defined and characterized by Isaacs and Patrick Walsh in the late 1980s. about 25 percent of men with prostate cancer have a family history of the disease, but only about 3 or 4 percent of men have an inherited, genetic form that involves mutated genes, which can be passed on by either parent. since then, Isaacs and colleagues had discovered several intriguing “prostate cancer genes,” but no male equivalent of the BrCa1 and BrCa2 mutations in breast cancer.)

The gene in question is named HOX B13 and in its normal form, it’s important in the development of the prostate before birth. When it is mutated, however, cell growth in the prostate is unchecked and cancer is a



Scientists William Isaacs, right, and Charles Ewing found that men who inherit the HOX B13 mutation are 10 to 20 times more likely to get prostate cancer than other men, and at a younger age.

common result. In the study, multiple members of four different families – and every one of the men who developed prostate cancer – turned out to have this mutation.

“This is what we have been looking for,” says Isaacs, *The William Thomas Gerrard, Mario Anthony Dubon and Jennifer and John Chalsty Professor of Urology*, and *The Dr. and Mrs.*

**The scientists knew a major gene mutation had to be there. More than 20 years ago, they knew it.**

**They just couldn’t find it.**

*Peter S. Bing Scholar.* His research has been generously supported by donors including Mr. P. Kevin Jaffe and the Peter Jay Sharp Foundation. “We have never seen anything like this before,” adds Walsh, a co-author of the study. “It all came together to suggest that this single change may account for at least a portion of the hereditary form of prostate cancer.” Among other implications, this discovery may lead to a genetic test that could help save lives as men who turn out to have this mutation begin regular screening, perhaps even starting as early as their thirties.

Together with colleagues at TGen in Arizona, the scientists studied genetic mate-

rial from the youngest men diagnosed with prostate cancer in 94 families who had participated in studies at Johns Hopkins and the University of Michigan. Each family was hard hit by prostate cancer, with several close relatives (brothers, or fathers and sons) affected. Next, working with scientists at Wake Forest University, the researchers looked for the same mutation among 5,100 men who had been treated for prostate cancer at either Hopkins or the University of Michigan. The mutation was found in 72 of the men. These men also were much more likely to have at least one first-degree relative who also had been diagnosed with prostate cancer, and to have an early age at diagnosis.

This particular HOX B13 mutation was identified in families of European descent. Two other mutations on the same gene were also found in families of African descent; black men are more likely to be diagnosed with prostate cancer at a younger age, and to have aggressive cancer that needs curative treatment. “More research is needed before we understand the significance of these mutations,” says Isaacs. “We need to continue studying HOX B13, and to expand our study to include larger groups of men.” Isaacs also plans to develop a mouse model with this mutation (see story on Page 18). Until these results have been duplicated by other institutions and the risk for carriers

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to develop prostate cancer confirmed with more certainty, this test will not be available for general use.

Neither Isaacs nor Walsh believes the search for genes linked to hereditary prostate cancer is over. Far from it; in fact, “the complex genetic architecture of prostate cancer, with both common and rare mutated genes playing a role in inherited susceptibility, may help explain why it has taken so long to identify genes such as HOX B13,” says Walsh. “It is likely that there are multiple, similar, rare but dangerous mutations that are responsible for hereditary prostate cancer, and that no one mutation will explain the majority of the cases. I believe we will find out that many roads lead to Rome.”

#### GENES AND PROSTATE CANCER:

## 26 Years of Genetic Discovery at the Brady

### 1986

Patrick Walsh, who has been seeing increasingly younger men with prostate cancer, is struck by how many of them have a family history of the disease. One of his patients, a 49-year-old man, has an unforgettable legacy: Every male in his family has died of prostate cancer: His father, his father’s three brothers, and his grandfather. Walsh, then Director of the Brady, launches the first of a series of genetic studies.

### 1990

A study of 691 of Walsh’s radical prostatectomy patients demonstrates that a family history of prostate cancer is a major factor that increases risk of the disease. Men who have a father or brother with the disease have a twofold higher risk, and this increases if there are three or more first-degree relatives affected.

### 1991

Based on the data collected in Walsh’s families, a study published in the *Proceedings of the National Academy of Sciences* demonstrates for the first time that the aggregation of

cases in families is caused by Mendelian inheritance of a rare gene.

### 1993

Based on the prior findings, the definition of hereditary prostate cancer (HPC) is developed, a definition that is used widely today: three or more first-degree relatives (father, son, brother), or three generations (grandfather, father, son), or two first-degree relatives if both are less than 55 years old. These are the families that are targeted for DNA analysis to search for specific mutations involved in the development of prostate cancer.

**An estimated 17,000 fewer men per year are diagnosed with metastatic disease today, compared to the pre-PSA era.**

### 1996

Using linkage analysis as a method to find genes causing prostate cancer (this has been compared to trying to find one misspelled word in 20 sets – each containing 20 volumes – of the *Encyclopedia Britannica*) Isaacs and colleagues report in *Science* magazine the first linkage between prostate cancer in families and a region of the genome located roughly in the middle on the long arm of chromosome 1. The scientists are optimistic that they will soon be successful in identifying genes like the BRCA1 and BRCA2 mutations in breast cancer. In 2002, they do identify mutations in two genes involved in inflammation, one on chromosome 1 (*RNASEL*, on the long arm of chromosome 1, a gene that codes for ribonuclease-L) and the other on chromosome 8 (*MSRI*, found on chromosome 8, which codes for macrophage scavenger receptor 1). But the effect of these genes on prostate cancer risk is small and variable from population to population. In all, Isaacs and colleagues toil for 16 years without success in finding a mutation that, if inherited, dramatically increases a man’s risk of developing prostate cancer.

### 2012

Success!

## Misfire: Bad Advice from a Government Task Force

For nearly 20 years, in this publication and its predecessor, *Prostate Cancer Update*, we have given you “all the news that’s fit to print” – everything we have been learning about prostate cancer, our clinical advancements and scientific discoveries. It has always been, and remains, cutting-edge information (like Bill Isaacs’ exciting discovery of a major prostate cancer gene – see Page 3). And the best thing for all of us here at the Brady Urological Institute is that the news has just gotten better over time.

With one exception. Recently, something happened that is not good news; in fact, it has the potential to be disastrous. In a move that has stunned and outraged those in the medical community dedicating ourselves to treating and curing prostate cancer, The United States Preventive Services Task Force (USPSTF) has recommended against PSA screening for prostate cancer. Its message to men: “Don’t worry about screening. If you’re diagnosed with prostate cancer, don’t worry about it. You probably won’t die of it.”

This is simply not true. If you’re a patient here at the Brady, you probably already real-

## The Bottom Line

PSA screening has saved tens of thousands of lives. To abandon it, in effect, is turning the clock back to the early 1990s, when 20 percent of men were diagnosed with cancer already in their bones, and one out of five men had metastases. There is potential for disaster if men stop getting PSA screening. The American Society of Clinical Oncology has rejected this recommendation. Instead, it has made the sensible decision to discourage PSA screening in men with a life expectancy of less than 10 years, but to advise men who are expected to live longer than 10 years to discuss the benefits and harms with their physician.

ize this; but we'll explain more in a moment. First, you need to know that the panel is made up of "independent scientists who are better able to objectively evaluate the literature without bias." *No urologists or other prostate cancer specialists were invited to participate.*

According to the panel, "healthy" men don't need PSA screening. We know that this is a bad idea, because we have already been there and done that. We lived through it, and for most men diagnosed with prostate cancer, the picture was not pretty. In effect, this decision sets the clock back to before the 1990s, when "healthy" men were diagnosed with cancer that was palpable – because there was no blood test to help detect it. Too often, these men were diagnosed when their cancer was too late to cure. (For a look at the numbers and the impact of the "nerve-sparing" radical prostatectomy on cancer control after PSA screening began, see illustrations on Page 6.)

Knowing the outcome of cancer in the days before PSA screening prompts a question that looms like the proverbial elephant in the room: Is this panel's recommendation about progress, or about saving money?

### Prostate Cancer 101

Some very basic facts about this disease: Prostate cancer is the most common cancer in American men and the second most common cause of cancer death. Because the cancer begins on the prostate's outer edges, it produces no symptoms until it is far advanced and too late to cure. It can be diagnosed with a rectal exam, but it has to have achieved a size big enough to be felt by a doctor – and often, by the time the cancer has grown this much, it has also spread past the confines of the prostate. Yet years before this happens – in a man who is still outwardly "healthy" – PSA is silently trumpeting the danger. Because of pioneering work led by Johns Hopkins, we know how to read PSA. We know at what level it should be, in men of every age; we know when its rise is fast enough to warrant a biopsy, and by looking at components of PSA, when its number is most likely due to benign enlargement. PSA is not perfect, but it has saved tens of thousands of lives. And thanks to PSA testing, we have proven that early diagnosis is everything. It is the cornerstone that has dramatically reduced death and suffering.

In 1991, before PSA testing became widespread, 20 percent of men with a new diagnosis of prostate cancer had a tumor that had already spread to their bone. *Today that number is less than 4 percent.* It's hard to imagine now, but in 1991, one out of five men had metastases. Today, it's one out of 25.

The effect on deaths is equally dramatic. Between 1994 and 2004, prostate cancer deaths plummeted 40 percent – more than for any other cancer in men or women. But what would have happened if PSA testing and effective treatment had not come along? Using the age-adjusted death rate from 1990 of 39.2 prostate cancer deaths per 100,000 men and applying it to 2007, there would have been 59,000 deaths. Instead, because the death rate fell to 23.5, there were 35,000 deaths. Thus, 24,000 fewer men died from prostate cancer in 2007 alone. Because advances in treatment have also played a role, scientists from the National Cancer Institute estimate that 40 to 70 percent of this reduction is the direct result of screening.

### Turning a Blind Eye to Lives Saved

Unfortunately, the USPSTF never mentions these figures, and makes no attempt to reconcile them with its recommendations. The scientists did use large, uncontrolled observations to look at the complications of surgery – but *not at the number of lives saved since PSA testing was introduced in the United States in the early 1990s.*

Also, the USPSTF recommendations are based on two trials with 10 years of follow-up – even though it is widely accepted that men with a lifespan of fewer than 10 years should not be screened or treated. So what should have been their conclusions? That men with a lifespan of less than 10 years should not undergo PSA screening. However, screening has been definitively shown to save lives for younger, healthier men.

The USPSTF ignores or fails to recognize that without PSA testing, a man will not know that he has the disease until he has symptoms, at which time the cancer is too far advanced to cure. In the absence of mammography, at least a woman can palpate her own breast to search for a lump. If the Task Force is trying to fix the downstream consequences of over-diagnosis and over-treatment, why not encourage funding agencies to enforce the National Comprehensive Cancer Network (NCCN) Guidelines for

diagnosis and treatment? Instead, it chose to deny healthy young men with asymptomatic, potentially deadly cancer the chance of cure. This is like removing all the scalpels in a hospital to prevent unnecessary surgery. If this recommendation is widely adopted by physicians and insurance companies, in the next five years we should expect to see 65-year old men arriving for their first PSA (in 1997 Congress mandated Medicare to pay for PSA testing) with advanced disease. Indeed, a recent study predicted that as a result of PSA testing there are 17,000 fewer men *per year* diagnosed with metastatic disease today, compared to the pre-PSA era.

On a more encouraging note, the American Society of Clinical Oncology has rejected the USPSTF recommendation. Instead, it has made the sensible decision to discourage PSA screening in men with a life expectancy of less than 10 years, but to advise men who are expected to live longer than 10 years to discuss the benefits and harms with their physician.

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## The Impact of Anatomic Radical Retropubic Prostatectomy on Cancer Control: 30 Years of the "Walsh Procedure"

Before 1982, not many men wanted to undergo radical prostatectomy, because the cure was considered as bad as, if not worse than, the disease. Impotence was universal, and incontinence was more common than not. The operation was also notorious for the excessive bleeding that went along with it. But then surgeon Patrick C. Walsh, M.D., discovered the location of the nerves responsible for erection. They were where no one had suspected – outside the prostate – and did not necessarily have to

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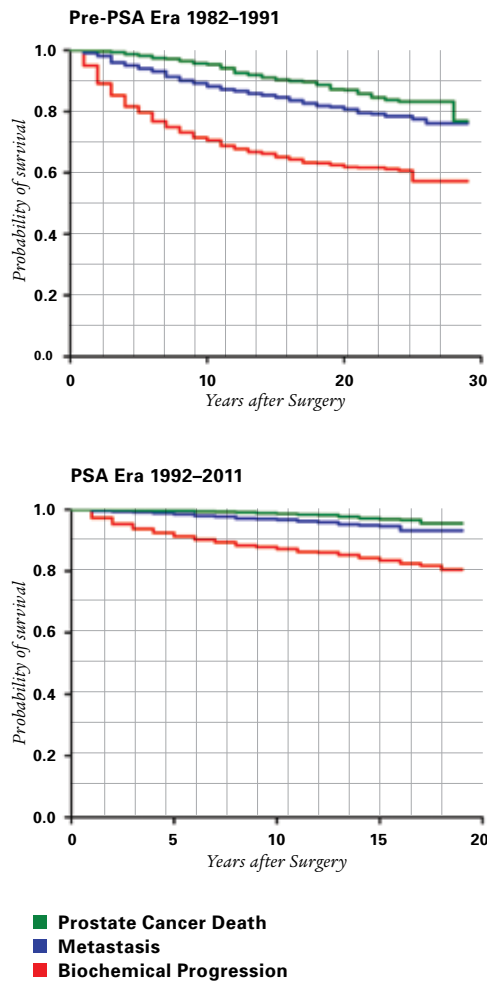


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be removed along with the prostate. He also developed techniques to create a “bloodless field,” to reduce the terrible blood loss and allow the surgeon better vision of the anatomic terrain during the procedure which, in turn, produced a dramatic reduction in incontinence as well as impotence. These discoveries marked the birth of the “nerve-sparing” radical prostatectomy, the “Walsh Procedure,” which has become the gold standard for treatment of prostate cancer.

**Patrick Walsh wants his patients to know that without their feedback – more than 50,000 PSA reports over the years – he wouldn’t be able to provide these results. “You sent them in and I added them to the database. As a result, it is possible to be more precise in charting the future for the next generations of men who will be undergoing surgery. This is a wonderful legacy that you have created.”**

At the 30-year anniversary of this landmark discovery, scientists Stacy Loeb, Walsh, Jeffrey Mullins, Zhaoyong Feng, Bruce Trock and Jonathan Epstein examined the results of 4,569 radical prostatectomies performed between 1982 and 2011 by Patrick Walsh at Johns Hopkins; their results will be published in the December 2012 *Journal of Urology*. “The average follow-up was 10 years,” says Loeb, now at New York University. “Our most important finding was that men treated after 1992, when PSA screening was introduced did much better than the men treated between 1982 and 1991. Because screening allowed men to be diagnosed earlier, men from the PSA era



*PSA recurrence, metastatic disease, and prostate cancer death have decreased dramatically in men treated in the PSA era (after 1992).*

were far more likely to have organ-confined-disease (72 percent versus 37 percent) and less likely to have involvement of the seminal vesicles and lymph nodes. As a result, PSA recurrence, metastatic disease and prostate cancer death occurred much less frequently among men treated in the PSA era.” These results are particularly timely in light of the recent controversial recommendation from the United States Preventive Services Task Force that PSA testing (see story on Page 4) should not be done.

Tumor stage and grade were also important factors in predicting the long-term

prognosis after surgery. “Based on this wealth of information and the lengthy follow-up, we now have long-term prognostic information that can be shared with patients,” she adds.

These results are in line with another recent study by Loeb and collaborators from the European Randomized Study of Screening for Prostate Cancer (ERSPC). In this large, randomized study, scientists found that men who had PSA screening had better outcomes after surgery than men who were not diagnosed through screening. “These studies both highlight how screening and curative treatment go hand in hand,” says Loeb.

In conclusion, “we found excellent long-term cure rates with contemporary anatomic radical prostatectomy,” Loeb says. “These results are encouraging for men who have undergone surgery for prostate cancer, showing a low risk of the disease spreading or causing death many years afterward.” The authors hope these historic data will also provide a useful benchmark for comparison with new forms of treatment.

Walsh notes that this study would not have been possible without the participation of his patients, “who faithfully reported their status year after year, giving us more than 50,000 PSA reports.” To his patients, he has this message: “You sent them in and I added them to the database. As a result, it is possible to be more precise in charting the future for the next generations of men who will be undergoing surgery. This is a wonderful legacy that you have created.”

## The Bottom Line

The study’s most important finding was that men treated after 1992, when PSA screening was introduced, did much better. Because screening allowed men to be diagnosed earlier, these men were far more likely to have organ-confined disease. As a result, PSA recurrence, metastatic disease and prostate cancer death occurred much less frequently among men treated in the PSA era.

## The PIVOT Study: No “Game-Changer” Flawed Study Results in Misleading Advice for Men Considering Surgery

The PIVOT Study (Prostate Cancer Intervention Versus Observation Trial), whose results were recently published in the *New England Journal of Medicine*, began in 1994, early in the PSA era. It was originally designed to be a large study involving 2,000 men who were randomly assigned either to radical prostatectomy or observation. The study itself was severely flawed. For one thing, it was statistically underpowered; the scientists recruited only 731 men, instead of the 2,000. (An editorial that accompanied this article stated that it would require 1,200 patients to fulfill the statistical goal that the study’s authors reported.) Also, although the study was designed to include only men with a life expectancy of at least 10 years, at the end of the study half of the participants had died of causes other than cancer, leaving only 171 men in the surgery group and 183 men in the observation group available for analysis at 10 years.

**The men in this study were so sick that 15 percent couldn’t walk, and within 10 years, half of them had died of causes other than cancer.**

But even worse was the fact that *in one-half of the men, cancer extended outside the prostate, making it difficult to cure.* And, although the authors deny it, the follow-up of 10 to 12 years was far too short to be conclusive in making recommendations for men with low-risk disease.

And yet, much of the news media took this story at face value. For example, the *New York Times* reported: “A new study shows that prostate cancer surgery, which often leaves men impotent or incontinent, does not appear to save the lives of men with early stage disease, who account for most of the cases, and many

of these men would do just as well to choose no treatment at all.” This study, the newspaper added, was “game-changing.”

If you have already undergone surgery, you might well have wondered, “what have I done?” Unfortunately, many young men with aggressive, curable disease will only remember this sound bite. Is this true? Sadly, no.

### Does this Apply to My Cancer, and My Potential to Benefit from Treatment?

The study was carried out at Veterans Administration centers, where the surgery is often performed by inexperienced residents. The average age of the men in this study was 67; only 10 percent of the men were younger than 60. Today, cancer is diagnosed sooner than it was then, and the great majority of men at diagnosis have no symptoms and curable disease. The men in this study were so sick that 15 percent couldn’t walk, and within 10 years, half of them had died of causes other than cancer.

The study’s authors concluded that “among men with localized prostate cancer detected during the early era of PSA testing, radical prostatectomy did not significantly reduce all-cause or prostate cancer mortality, as compared with observation.” This study is a straw man; its authors wanted to mislead readers by suggesting that their findings apply to all men with prostate cancer – when in fact, their results only apply to men who are older or in poor health, and this finding is far from newsworthy. For three decades, we have said that men who have a life expectancy of 10 years or less should not undergo surgery.

The study’s authors never conceded that their observations should not be applied to younger men. But an ever-growing volume of evidence shows that in men with low-volume cancer, progression continues for many years. For example, in a study from Sweden of men with very small cancers who were treated with observation alone, death rates from prostate cancer remained very low (15 per 100,000 persons) for the first 15 years – but beyond that point, they skyrocketed (to 44 per 100,000 persons), and nearly all these men eventually died from prostate cancer. The PIVOT authors did not admit this likelihood in their study. Because only 26 men who underwent surgery and 36 men in the observation group were alive at 14 years, this

study will never have follow-up long enough to answer this question. With all of these shortcomings, it is surprising that they were able to demonstrate some significant benefits of surgery: There was an overall 60 percent decrease in the risk of metastases and a reduction in prostate cancer deaths in men who had a PSA greater than 10 ng/ml or who were in the high-risk category who underwent surgery.

**All the PIVOT study tells us is that for a man who has a life expectancy of 10 years or less and who has low-volume disease, surgery is not an option. This is old news.**

All the PIVOT study tells us is that for a man who has a life expectancy of 10 years or less and who has low-volume disease, surgery is not an ideal option. This is old news, and is far from being a “game-changer.” The information in this article is simply not good enough to be of help to an otherwise healthy man in his forties, fifties, or early sixties trying to figure out what he should do.

## The Bottom Line

The PIVOT study provides no useful information for an otherwise healthy man in his forties, fifties, or early sixties who is contemplating whether he should undergo surgical therapy.

## Special Lab Mice Develop Prostate Cancer That's Much Closer to The Kind Men Get

Oncologist Bill Nelson, M.D., Ph.D., head of the Sidney Kimmel Comprehensive Cancer Center, and *The Marion I. Knott Professor of Oncology*, has been studying an enzyme called GSTP1 (glutathione S-transferase  $\omega$ ) for more than a decade. In fact, it is due to his pioneering work, done with colleagues Angelo De Marzo, Bill Isaacs, and others, that we know so much about why this enzyme is so important in the development of prostate cancer. GSTP1 is a genetic “fire extinguisher” that cleans up toxins in cells. It takes dangerous free radicals – produced by many of the foods we eat – and turns them into harmless, water-soluble products,

**As much as scientists have learned about GSTP1, they have not been able to study it in the laboratory as effectively as they wanted to – until now.**

preventing the ravages of oxidative damage.

GSTP1 is also one of the first lines of defense to be knocked out in prostate cancer. Without GSTP1's damage-controlling effects, cancer has a far easier time taking hold and overpowering the body's ability to fight it. As much as scientists have learned about GSTP1, they have not been able to study it in the laboratory as effectively as they wanted to – until now. “We have created a strain of mouse that has human GSTP1 genes,” says Nelson. “These are the genes that direct the production of enzymes that protect normal cells against cancer-causing chemicals, including those that appear in overcooked meats, and against oxidative damage.” Nelson and colleagues Matthew

Vaughn, Debika Biswal-Shinohara, Nicole Castagna, Jessica Hicks, George Netto, Angelo De Marzo, Traci Speed, Zachery Reichert, Bernard Kwabi-Addo, Colin Henderson, C. Roland Wolf, and Vasan Yegnasubramanian recently published this research in the journal, *PLoS One*.

Why was this specialized mouse needed? Because humans, literally, are a “different animal” when it comes to how we process food and other things. “In mice and other mammals, genes that carry the blueprints for the various enzymes that are involved in the metabolism of drugs, toxins, carcinogens, and other reactive chemicals tend to be regulated differently,” Nelson explains. “For example, mice exhibit different side effects or complications to drug and chemical exposures than humans do.” These differences can often be crucial. Nelson cites one classic research example in which the difference in species produced devastating consequences: “When pregnant mice were treated with thalidomide, it did not cause problems in their offspring. But when pregnant women took thalidomide (as a treatment for morning sickness), it caused severe and terrible birth defects.”

In men who develop prostate cancer, the loss of GSTP1 function is “the most consistent acquired gene defect,” says Nelson. “What interested us, of course, was that the mouse *Gstp* genes were entirely different in the mouse prostate than human *GSTP* genes were in the human prostate.” To develop a “humanized” mouse model of this important event in the formation of cancer, “we introduced, via genetic engineering, the human *GSTP1* gene into a mouse that had its own *Gstp* genes deleted.” In the research paper, Nelson and colleagues demonstrated that “in the prostate and every organ in the body where the human and mouse genes were expressed differently, these mice showed the human pattern.” In the liver, the result was a different response to an overdose of acetaminophen (Tylenol). The group's current work suggests that these mice will develop a type of prostate cancer that is much more like human prostate cancer.

## Nerve Stimulation May Help Preserve Erectile Function after Radical Prostatectomy

As its name suggests, the nerve-sparing radical prostatectomy is designed to preserve, as much as possible, the bundles of nerves on either side of the prostate that are responsible for erection. If cancer is not nearby and these nerves can be spared, a careful surgeon takes extreme care to treat them gently. However, these nerves do not have the protective coating (the myelin sheath) that insulates larger nerves, and this makes them vulnerable to injury from heat and stretching. For this reason, says neuro-urologist Arthur Burnett, M.D., M.B.A., and *The Patrick C. Walsh Professor of Urology*, these nerves often take



Arthur Burnett, right, with Urology fellow Robert Segal: Because the nerves lack protective insulation, they are vulnerable to injury during surgery.



a hit simply because neighboring tissue is being removed – imagine windows shattering throughout a city block after a grenade goes off in a parked car. “It is evident that these nerves still sustain a ‘shock effect’ during surgery despite our best precautions,” he says. “The result is that erection recovery after surgery is often delayed.”

Burnett’s laboratory, which has made many important discoveries in the physiology of erection and in developing strategies to give extra protection to these nerves, has been working to “consider how the nerves can be induced to make a more rapid functional recovery,” he explains.

Is it possible that these nerves could somehow be jump-started – stimulated somehow, to encourage regeneration? In preclinical studies, Burnett and colleagues have investigated using a chronic implantable nerve stimulation system; more recently, they have focused on an approach that does not require implantation, which works externally to stimulate nerves to produce an erection. This research was recently published in the *Journal of Sexual Medicine*.

“The investigative work has led to the development of an external vibration stimulatory device that may be applied under a specified protocol after surgery,” Burnett says. “Our preliminary results suggest a likely benefit of this treatment. A definitive clinical trial is currently under way.”

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## Over-Treating Prostate Cancer

Do some men receive treatment for prostate cancer that they don’t need? Absolutely, says urologist H. Ballentine Carter, M.D., whose pioneering “Active Surveillance” program of rigorous monitoring has set the standard for helping some carefully selected men with small-volume, slow-growing prostate cancer put off, or avoid altogether, surgery or radiation therapy. Carter has also dedicated the last two decades of his career to learning the intricacies of PSA; he coined the term “PSA velocity” – a means of watching PSA’s rise over time, and understanding when its pace might signal cancer. At the same time,

it was Carter’s research that discovered that men with very low PSA levels can have high-risk cancer, that men who are in the Active Surveillance program need periodic biopsies every one to two years – and that even then, there is no guarantee that cancer might not somehow slip outside the prostate.

Carter tries very hard to find balance between treating prostate cancer that probably isn’t going to cause trouble, and not treating cancer that shows signs of becoming dangerous. His work is more important than ever, with the U.S. Preventive Services Task Force’s recent recommendation that men don’t need PSA screening (see Page 4), and the PIVOT investigators advising against surgery (see Page 7). Also, “the National Institutes of

**The ultimate choice for treatment depends on a man’s personal preferences. “Would you rather live knowing you have cancer, or would you rather put up with the possible side effects of treatment?”**

Health convened a State of the Science conference to address the topic of active surveillance as a means of reducing prostate cancer over-treatment, and concluded that this approach is underutilized today,” he notes. “Most experts, regardless of their perspective, agree that over-treatment of prostate cancer needs to be addressed.” Carter believes the answer lies in an individualized approach to patient care. In two articles recently published in the *Journal of Urology*, he shared what he and colleagues have found.

### Low-Risk Prostate Cancer

What is low-risk prostate cancer? It either is a very small nodule, or is too tiny even to be felt on a digital rectal exam; its Gleason score is 6 or less; and it’s associated with a PSA lower than 10 ng/ml. Working with Carter, David Liu, who is training to be a medical oncologist, designed a computer model to compare the effectiveness of surgery or active surveillance in men with low-risk prostate cancer. He looked at the years of life gained,

and also the quality of those extra years based on potential side effects of treatment – a measure called “Quality-Adjusted Life Years” (QALY). “David found that for men up to 74 years who were in excellent health, surgery was preferable,” (with greater QALYs), Carter explains. “But for men in poor health over age 54, surveillance was preferable. For men in average health, who make up half of the population, surveillance was preferable over age 67.” Still, he adds, the ultimate choice depends on a man’s personal preferences. “Would you rather live knowing you have cancer, or would you rather put up with the possible side effects of treatment? Since 90 percent of men in the U.S. who are diagnosed undergo some type of treatment for their cancer, these findings suggest that a large proportion of men should consider their choice carefully. This study helps men make a more informed choice.”

### Should the Treatment be Surgery?

In the second publication, Carter worked with Jeff Mullins, a urology resident. “Jeff set out to determine what proportion of men undergoing surgery at Johns Hopkins had a diagnosis of low-risk prostate cancer. Looking back from 1983 to 2010, he found that only 8 percent of the more than 19,000 radical prostatectomies performed were in men over age 65 with low risk prostate cancer,” Carter says. About one in three of these 8 percent turned out, after the pathologist examined the prostate specimen, to have more extensive disease than the surgeon expected based on the biopsy, PSA, and rectal exam. “These are the men more likely to have benefited from an operation,” says Carter. But in contrast to our experience at Johns Hopkins, in the U.S., instead of 8 percent, about 40 percent of men between ages 65 and 74 with low-risk prostate cancer undergo surgery. This probably reflects our view that older men with low-risk prostate cancer should carefully consider whether or not surgical treatment is necessary and the right choice for them.

This year, Carter was elected to the Board of Trustees of the American Board of Urology. This distinguished organization has the responsibility of protecting the public, ensuring the high-quality, safe, efficient and ethical practice of urology by establishing and maintaining standards of certification for urologists.

## Bad Equation: Infection Plus Bad Diet Leads to Cancer?

Several years ago, scientist Bill Nelson, M.D., Ph.D., now director of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, introduced the readers of this publication to a funny little word: “PhIP.” It sounds so harmless, but PhIP, an abbreviation for a long chemical name, is something known as a pro-carcinogen. Not necessarily bad in itself, it can be metabolized to something more dangerous: a chemical that attacks and mutates DNA and is known to cause prostate, colon, and breast cancer in rats.

Unfortunately for those of us who love charred meat, we create carcinogens, or cancer-causing agents, with every steak, hamburger, or piece of chicken we grill or fry – and PhIP is one of them. In 2007, Nelson and pathologist Angelo De Marzo, M.D., Ph.D., reported in *Cancer Research* that when rats are exposed to PhIP, DNA mutations occur in the prostate. Recently, Karen Sfanos, Ph.D., who was a postdoctoral fellow in De Marzo’s lab and since has joined the faculty, has added striking new findings to our knowledge of PhIP. Her work brings together not only the groundbreaking stud-

ies by Nelson and De Marzo of the role of diet in prostate cancer, but the pioneering ideas being carried out by Nelson, De Marzo, William Isaacs, *The Dr. and Mrs. Peter S. Bing Scholar*, Elizabeth Platz, *The Martin D. Abeloff, M.D. Scholar in Cancer Prevention* and others at the Brady involving inflammation and the start of prostate cancer.

In rats, Sfanos has found that if the prostate becomes infected at a time when the diet also includes PhIP, this “combination of environmental insults” can encourage the development of prostate cancer. The rat prostate is a small gland, but it has different areas, or lobes, that are made up of different types of tissue. In the PhIP-treated rats, prostate cancer develops only in the ventral lobe. In men, cancer occurs mainly in what’s called the peripheral zone of the prostate. “De Marzo’s group found that after exposure to PhIP, there was also an increase in

**Unfortunately for those of us who love charred meat, we create carcinogens, or cancer-causing agents, with every steak, hamburger, or piece of chicken we grill or fry – and PhIP is one of them.**

stromal mast cells and macrophages – inflammatory cells that play a key role in immune defenses – only in the ventral lobe of the rat prostate,” says Sfanos. “This finding, that infiltration of inflammatory cells was restricted to the very same lobe of the prostate that developed cancer, suggests that inflammation may play a role in cancer caused by PhIP.”

To explore the association between inflammation in the prostate, PhIP and cancer, Sfanos and colleagues decided to see whether chronic inflammation caused by bacterial infection could make a difference in rats that had consumed PhIP. She used a specific strain of *E.coli* that was isolated from a patient with chronic prostatitis/chronic pelvic pain syndrome by Anthony Schaeffer, M.D., of Northwestern University, and further studied by Brady urologist Edward Schaeffer, M.D., Ph.D. “What we unexpectedly found was that the *E. coli* infection in the prostate and inflammation in the PhIP-treated rats appeared to have a systemic effect,” says Sfanos. “This led to an increase in the development and progression of cancer in multiple sites, including the skin and the gastrointestinal tract.”

Even more remarkable was that the rats that received the “double whammy” of *E. coli* and PhIP fared worse than rats that received PhIP alone. “The animals that received both PhIP and *E. coli* developed more precancerous lesions on average within the prostate compared to the animals that had PhIP alone,” says Sfanos. This difference in the development of precancerous lesions within the prostate may have been even more pronounced, she adds – except animals treated with PhIP plus *E.coli* died sooner. They “exhibited a marked decrease in median survival due to a twofold increase in the development of *invasive cancers at other sites*. This phenomenon of an increase in the development and progression of cancer at multiple sites may have been mediated in part by an elevated level of cytokines in the blood of the animals caused by the infection.” (For more on cytokines, see story on Page 13.) Sfanos believes that this rat model may be helpful in future studies of the bad combination of diet and infection in the development of prostate and other forms of cancer.

Also taking part in this study were Kirstie Canene-Adams, Brian Simons, William Nelson, and Charles Drake.



Karen Sfanos and Angelo De Marzo: Inflammation may play a role in cancer caused by PhIP.

## With Help from a Robot, a Better Prostate Biopsy

Nobody loves prostate biopsies – certainly not the men getting them, but the doctors who perform them know that despite their best efforts to sample the entire prostate, they may miss cancer.

More than 1.2 million prostate biopsies are performed each year in the U.S. using transrectal ultrasound as the guidance system. The problem is that “standard gray-scale ultrasound imaging provides minimal cancer-specific information in regard to localizing tumors,” says Dan Stoianovici, Ph.D., Director of the Urology Robotics Laboratory and *The Virginia and Warren Schwerin Scholar*. The urologist performs the biopsy according to a template and hopes that by sampling bits of tissue throughout the prostate, if cancer is present it will be detected. “Standard biopsies typically have low sensitivity and low negative predictive value.” In other words, if the biopsy does not show cancer, this doesn’t necessarily mean that it isn’t there. The biopsy could have just missed the mark. Or, it may find small lesions that are unlikely to cause problems. “These uncertainties may contribute to disease over-treatment,” Stoianovici continues.

Another imaging technology, MRI of the prostate, provides better pictures but is hard to use as a means of guiding a needle. Stoianovici and colleagues are working to develop technologies for biopsies that target suspicious lesions depicted in MRI. The Urology Robotics Laboratory has developed a new MRI-Safe robot for transrectal prostate biopsy – done in the MRI scanner itself. “The robot presents three degrees of freedom,” says Stoianovici, “two for orienting a needle-guide and one for adjusting the depth of needle insertion.” Animal tests conducted at the Memorial Sloan-Kettering Cancer Center have shown the feasibility and accuracy of the approach.

This research, supported by a grant from the Prostate Cancer Research Program of the Department of Defense, was presented at the American Urological Association’s annual meeting in 2012 and won an Outstanding Paper Award from the Engineering and Urology Society.

### HUMAN VERSUS ROBOT: WHO CAN BIOPSY BETTER?

**Speaking of better prostate biopsies: During your basic prostate biopsy a physician, guided by transrectal ultrasound, uses a needle to take core samples of tissue throughout the prostate. “Although several biopsy templates have been proposed, it is unknown how accurately biopsy samples are obtained by a physician,” says Brady urologist Misop Han, M.D. In a recent study using a biopsy simulation system, Han and scientist Dan Stoianovici, Ph.D., compared humans and robots. Specifically, they asked, who’s better at performing an accurate and reliable biopsy: Experienced urologists or a newly developed robot? This study will be published in the Journal of Urology.**

**“We found that urologists did worse biopsies compared to the robot,” says Han. “The biopsied samples obtained by urologists were often clustered and missed some portions of the prostate. Meanwhile, the robot closely followed the assigned biopsy template. Most importantly, we found that the robot most likely will detect more prostate cancer than experienced urologists.”**

**Han believes that robotic assistance, along with a better biopsy template, has the potential to improve the accuracy and reliability of prostate biopsy in the future. The scientists plan to perform a clinical study to test and confirm their theory.**

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## What Younger Men Choose, and Why

When it comes to prostate cancer, you’re on the young side – age 47. You’re otherwise healthy. Your cancer has been caught early, and is considered curable. This is a good problem to have. Now, the hard part: How should it be treated?

If you’re having a tough time making this decision, you’re not alone, and it may help to know how other guys in the same boat figure out what to do. Recently, an interdisciplinary group at the Brady, led by pathologist Jonathan Epstein, M.D., *The Rose-Lee and Keith Reinhard Professor in Urologic Pathology*, asked

nearly 500 men under age 50, diagnosed with Gleason score 6 disease, about their treatment decision-making. The results of their study were published in the journal, *Prostate*.

Out of 493 men, 81 percent (397) chose surgery; nearly 11 percent (52) chose radiation, and just over 5 percent (26) chose active surveillance. “We found that men with at least some college education or an annual income of \$100,000 or greater were more likely to consult three or more doctors,” notes Epstein. “Social support was very important. More than half of the patients consulted their family, spouses and friends before making their decision.” The most influential source of information for these men was “doctor’s recommendation,” although this was of slightly less importance in the active surveillance group. Many men went online to do research, as well; the Internet was the second most frequent source of information.

### How do other men decide which treatment is best?

“According to the patients, the most common reason to choose surgery over other forms of treatment was that it provided the best chance of cure,” says Epstein, although “patients in our study reported their concern over side effects as the reason for choosing active surveillance.” Men who chose radiation therapy cited its “less invasive nature” as their primary reason. Men with higher income and higher education also said they considered sexual function to be a more important factor in their treatment choice.

Only 2 percent of the men in this study preferred to have a passive role in the decision-making. “Informed decision-making by myself based on information” was preferred more by men who chose radiation and active surveillance, while “shared decision-making between my physician and myself” was preferred more by surgery patients.

Interestingly, the great majority – 89 percent – of the men in the study said they did not regret their decision. “We found no difference in satisfaction levels among the men in different treatment groups.” Abhinav Sidana, David Hernandez, Zhaoyong Feng, Alan Partin, Bruce Trock, and Surajit Saha also participated in this research.



## How the Gordian Knot's Solution May Help Kill Prostate Cancer Cells

Remember the legend of the Gordian knot? It was so intricate that no one could figure out how to untie it, until one day Alexander the Great came to town and solved the problem his own way: He simply cut it with his sword.

Michael Haffner, M.D., has discovered a similar story happening with hormones in prostate cancer. Male hormones, called androgens, help prostate cancer cells grow and survive using a complex network of chemical signals. "Recently we have uncovered a novel and striking aspect of androgen signaling," says Haffner. It turns out that "these hormones can induce breaks in the DNA of prostate cancer cells. This hormone-triggered process is likely mediated by an enzyme called TOP2B, which can untangle knots in the DNA by simply cutting the DNA molecule." Snip! and suddenly, it's a lot easier to undo one of these DNA snarls.

In earlier work published in *Nature Genetics* Haffner, together with Srinivasan Yegnasubramanian, William Nelson and other Hopkins investigators found that activity of the TOP2B enzyme can lead to gene defects. Now "we have also uncovered that androgens can specifically induce DNA damage in prostate cancer cells," Haffner adds. He and colleagues are investigating the biological role of androgen-induced breaks in the DNA "and more importantly, exploring the possibility of using these breaks to kill prostate cancer cells." In laboratory experiments, the investigators are sending short pulses of androgens to induce DNA damage in prostate cancer cells. "Using this approach in combination with other treatments that block repair processes of androgen-induced DNA breaks, we hope to develop a highly specific therapy for advanced prostate cancer."

For his work on the role of androgen-induced DNA breaks in prostate cancer, Haffner has received the prestigious W. Barry Wood, Jr. Award, given to young investigators at Johns Hopkins for outstanding biomedical research. He also has received a

Young Investigator Award from the Prostate Cancer Foundation.

## Discovered: How Advanced Cancer Cells Outwit Hormonal Therapy

Hormonal therapy can be effective for many years in controlling advanced prostate cancer. But it does not keep cancer in check forever. One reason is that as the cancer grows and changes, it develops cells that become resistant to male hormones, also called androgens. Hormone-resistant, also called "castration-resistant," cancers are very difficult to kill.

Now, scientist Jun Luo, Ph.D., has discovered a major secret to advanced cancer's evolution: The androgen receptor – a genetic lock, for which androgens are the key – is rendered useless. Imagine a key, perfectly suited for a particular lock – and suddenly, the keyhole is missing.

In exciting work published in the journal, *Cancer Research*, Luo and colleagues have discovered that some advanced cancer genes splice, and when they do, they shed the androgen receptor binding site – creating cancer cells that cannot be affected by hormones, because they no longer speak that language. There is no lock for the key. In other words, some advanced cancer cells evolve in such a way that they're one step ahead of the drugs designed to kill them.

"New drugs developed for the treatment of castration-resistant prostate cancer, such as abiraterone, are designed to suppress signaling of the androgen receptor," says Luo. "Specifically, these drugs target one particular area of the androgen receptor called the ligand-binding domain. But when these variant cells evolve, they don't have that particular domain." Because these streamlined cancer cells don't have the intended target of the drugs designed to kill them, they are suddenly "drug-resistant."

"Indeed," says Luo, "as prostate cancer cells adapt to these drugs, they shift to produce more of these variant cells, and their

**Luo and colleagues have discovered that some advanced cancer genes splice, and when they do, they shed the androgen receptor binding site – creating cancer cells that cannot be affected by hormones, because they no longer speak that language.**

whole mechanism of sustaining cell growth changes, as well." These rapidly adapting prostate tumor cells escape hormonal therapy unscathed. "What we hope to do next is to learn how frequently and how quickly this molecular shift occurs in men receiving hormonal therapy, and work with others to develop new ways to overcome this drug resistance."

## The Very Latest Partin Tables

They have been called the next best thing to virtual surgery. The Partin Tables were developed by Alan Partin, M.D., Ph.D., Director of the Brady Urological Institute, and *The David Hall McConnell Professor in Urology*, and Patrick C. Walsh, M.D., *University Distinguished Service Professor of Urology*, after they studied the course of prostate cancer in hundreds of Walsh's radical prostatectomy patients at first, and later expanded to include thousands of men who underwent radical prostatectomy at Johns Hopkins. These tables use clinical features of prostate cancer – Gleason score, PSA level in the blood, and clinical stage – to predict whether a man's tumor will be confined to the prostate. For decades, they have helped men and their doctors worldwide to predict the definitive pathological stage before treatment, so they can determine the treatment that is best for them. Over the years, the Tables have been updated to reflect the improvement in cancer control that has come in the "PSA era" with increasingly earlier diagnosis. Today, most men are diagnosed

with a lower PSA, lower clinical stage, and higher likelihood of harboring organ-confined tumors than men diagnosed with prostate cancer in the pre-PSA era, before 1992.

In these updated Tables, the findings came from 5,629 consecutive men who underwent radical prostatectomy and staging lymphadenectomy at Johns Hopkins between 2006 and 2011. The results were published in the *British Journal of Urology-International (BJUI)* and will be available for men and urologists worldwide, including on the Brady website at <http://urology.jhu.edu>. Taking part in this research were John Eifler, Zhaoyong Feng, Brian Lin, Michael Partin, Elizabeth Humphreys, Misop Han, Jonathan Epstein, Patrick Walsh, Bruce Trock, and Alan Partin.

"It has been very interesting to see how, since PSA screening was introduced in the early 1990s, the extent of disease for men with prostate cancer has slowly changed over time and now seems to have stabilized," notes Partin. "Also, subtle changes to the Gleason scoring system, (which narrow the scope of Gleason pattern 3 and widen the scope of Gleason pattern 4) have made the system

### Good news: Gleason 8 disease is more like Gleason 4 + 3 disease.

more accurate, and these were not considered in previous editions of the Tables."

The recent analysis demonstrated that "most men with Gleason 3+3 disease and many with Gleason 3+4 disease do not require pelvic lymph node removal during radical prostatectomy," Partin continues. "Also, traditionally men with Gleason 8, 9, or 10 disease have been considered high risk, though we found that men with Gleason 8 disease were closer in the extent of their tumor to men with Gleason 4+3 disease, rather than men with Gleason 9 and 10." Men with Gleason 8 disease, he adds, were much less likely to have lymph node involvement than men with higher Gleason scores. This is good news; in the past, men with Gleason 8, 9, and 10 disease all tended to be lumped into the same category.

"Clinicians should use these updated tables when counseling patients on the extent of their disease, and to help determine who would likely benefit from removing the lymph nodes during radical prostatectomy."

## An Inflammatory Question

For several years now, a multidisciplinary team of investigators at Johns Hopkins has been trying to figure out whether inflammation (and the body's immune response) has anything to do with prostate cancer. Several findings suggest that it does; for example, pathologists Angelo De Marzo and Jonathan Epstein have identified and characterized a type of inflammation found in biopsied prostate cells that seems to be a precursor to PIN (prostatic intraepithelial neoplasia), a type of "funny-looking" cells often found near cancer cells. Geneticist William Isaacs is studying genes related to the body's ability to fight inflammation that may be disabled in cancer. Oncologist William Nelson has spent years looking at the oxidative damage to cells caused by certain foods, and investigating possible steps between this oxidative damage, inflammation and cancer.

And epidemiologist Elizabeth Platz, Sc.D., M.P.H., *The Martin D. Abeloff, M.D. Scholar in*



*Elizabeth Platz and Nrupen Bhavsar: Interleukin-10 may help protect against prostate cancer by blocking inflammation.*

*Cancer Prevention* has led several important studies focusing on inflammation, including looking at the role of non-steroidal anti-inflammatory drugs (NSAIDs) as possible preventive agents in prostate cancer, and studying the potential of statin drugs, which lower cholesterol and are anti-inflammatory, to also lower the risk of developing prostate cancer. Recently, Platz and colleagues have conducted studies probing possible links

**Men who have higher levels of a naturally occurring chemical called interleukin-10 have a lower risk of developing prostate cancer, and of having it come back after treatment.**

between immune system-related factors and prostate cancer.

Part of their research has focused on a naturally occurring chemical called interleukin-10 (IL-10). This is a cytokine, an anti-inflammatory agent that regulates the body's ability to fight off countless foreign invaders including germs, pollen, and even cancer. Her team recently reported that men who produce more IL-10 were associated with lower risks of prostate cancer developing and recurring after treatment. Platz speculates that IL-10 may help protect against prostate cancer by blocking production of inflammatory agents. It also may put

up roadblocks that hinder cancer's ability to spread beyond the prostate.

With support from the Patrick C. Walsh Prostate Cancer Research Fund, the investigators' next step was to look for a link between the risk of prostate cancer and blood levels of IL-10 or other cytokines, measured months to years before the diagnosis. The A. Ross Myers family donated the money that supported this project.

"We studied 268 men with prostate cancer and 268 men without the diagnosis," says Platz.

"All of these men were participants in the CLUE II cohort study of Washington County, Maryland. They enrolled in the study back in 1989 and provided a blood specimen, and they've been followed ever since."

Platz and colleagues found that while blood levels of IL-10 were about the same in men with prostate cancer and in men without, men of normal weight who had more

*[continued on page 14]*

[continued from page 13]

IL-10 had a lower risk of prostate cancer. Interestingly, there seemed to be no such link in men who were overweight or obese. However, in all men, heavy or thin, the risk of prostate cancer was also lower when higher levels of some other cytokines were present.

**Maybe one day, if scientists can boost the levels of the body's most promising anti-inflammatory agents, they can help keep cancer from starting, or help stop it from spreading.**

Based on the evidence from this study, Platz and colleagues hope to learn more about how IL-10 and other cytokines help protect the body from cancer. It may be that one day, if they zero in on the most promising anti-inflammatory agents, scientists will be able to boost these levels in men with and without cancer, and that this may help keep cancer from starting, or help stop it from spreading.

This work was also conducted by Nrupen Bhavsar, a post-doctoral fellow, Alan Meecker, Sarah Peskoe, Charles Drake, Angelo De Marzo, William Isaacs, and Jay Bream, a Johns Hopkins Bloomberg School of Public Health expert in the biology of IL-10.

## New Marker May Spot More Aggressive Prostate Cancer

Two men may have the same Gleason score, PSA, and clinical stage of cancer. But it's possible that one of them has a more aggressive tumor – one that is more likely to come back after surgery. That man, and his doctors, would give anything for this information up front. Scientist George Netto, M.D., is working to make that happen. With collaborators at the departments of Urology,

Oncology and Pathology and the Bloomberg School of Public Health, he has been evaluating the role of a new potential prognostic biomarker, called PTEN, in prostate cancer.

PTEN, a protein molecule, helps keep rampant tumor growth in check by controlling a key pathway responsible for cell growth and metabolism in cancer. The scientists studied multiple tumor cores from more than 700 prostate cancer patients at the Brady. Tissue samples were arrayed on a set of 16 slides and analyzed using a special antibody that targets the PTEN molecule. Their study, published in the *Journal of Modern Pathology*, showed that when the PTEN protein was diminished or missing, there was a higher likelihood that a man's prostate cancer would come back after surgery. "Such studies performed at our institution could have significant implications on our future ability to stratify management of prostate cancer patients," says Netto, "and make treatment more personalized based on a man's individual, predicted risk of future cancer behavior."

## Having More Biopsies Doesn't Cause Extra Complications

Maybe you're a candidate for the Active Surveillance program, and it all sounds ideal for your needs – except for those pesky follow-up biopsies. Maybe you're worried that your prostate will turn into a pincushion, and maybe you'll even wind up in the hospital.

A lot of men worry about complications from having repeat prostate biopsies. But results from a new Brady study that involved thousands of men are reassuring: "Don't worry, because the risk of complications is very slight," says urologist Edward Schaeffer, M.D., Ph.D., Director of International Urology and Co-Director of the Prostate Cancer Multidisciplinary Clinic.

In an earlier study of first-time biopsies, Schaeffer and colleagues H. Ballentine Carter, M.D., and Stacy Loeb, M.D. (now at New York University), reported an increased

risk of hospitalization that was "attributable specifically to infectious complications," says Schaeffer. The results of this study prompted two things: One was a series of steps to make biopsies safer. "Based on the observations from these studies," he notes, "we worked with infectious disease experts at Hopkins to develop methods to screen for and reduce infectious complications after prostate biopsy." In a rectal exam, Hopkins urologists now routinely screen men for potentially dangerous bacteria before a needle ever touches their prostate: "We check the rectum for resistant bacteria," says Schaeffer, "and if it's present, we can modify

**"We know there are some risks associated with prostate biopsy, but this risk does not appear to increase with each biopsy."**

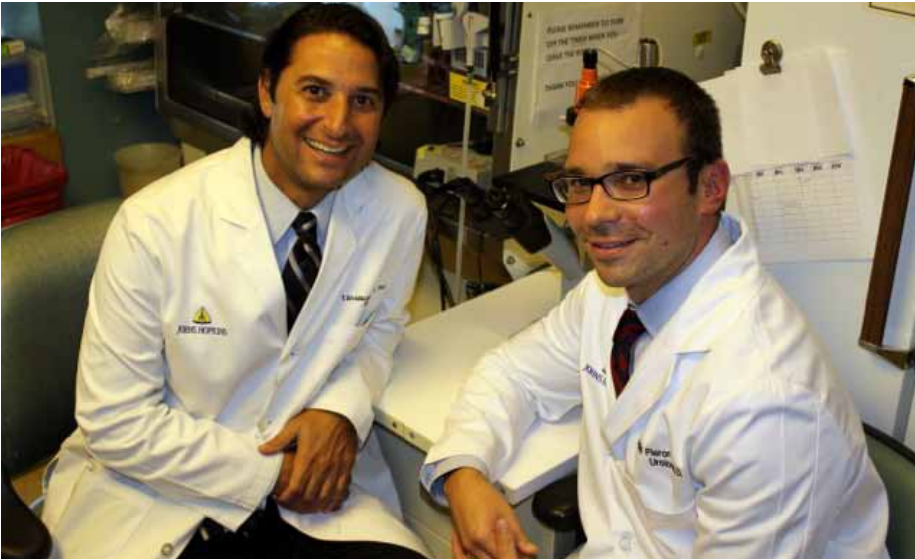
the antibiotics a patient takes ahead of time. This makes the biopsy process safer for all men undergoing this procedure."

The other major action that followed this study of first-time biopsies was a much larger study, to assess the risk of complications in men who receive one or more follow-up biopsies. "We looked at more than 13,000 men who underwent a single prostate biopsy, and then we looked at 3,640 men who had multiple prostate biopsies," says Schaeffer, "and examined the frequency of complications between these two groups."

The investigators found that compared to men who had never had a biopsy, men who underwent repeat prostate biopsies had only a slightly increased risk of hospitalization. "Fortunately, in the men who had additional biopsies there was no greater risk of serious complications (requiring hospitalization) compared to the initial biopsy," Schaeffer says.

Carter, who designed and directs the Active Surveillance program, says, "This is an important observation for our patients in Active Surveillance. We know there are some risks associated with prostate biopsy, but this risk does not appear to increase with each biopsy."





*Trinity Bivalacqua and Philip Pierorazio: Men with positive lymph nodes found in surgery can live for many years without metastases. The men in this study were treated primarily with surgery alone.*

## Double Good News for Men with Cancer-Positive Lymph Nodes

Although this is a story about prostate cancer that has spread to the lymph nodes, there is double good news that we are happy to report here. The findings come from a recent study of 30 years' worth of surgeon Patrick Walsh's radical prostatectomy patients who turned out to have clinically localized cancer with positive lymph nodes. The study, conducted by *Prostate Cancer Team Scholar* Trinity Bivalacqua, M.D., Ph.D., and urology resident Philip Pierorazio, M.D., looked at men diagnosed in the "pre-PSA" era, before 1992, as well as men whose cancer was found through PSA screening.

The first bit of good news is that the number of men diagnosed with prostate cancer in their lymph nodes has dropped from as many as 14 percent during the pre-PSA era, to about 4 percent in the early years of PSA screening, to a current low of about 1 to 2 percent. "Regular PSA screening has not only decreased the number of men being diagnosed with node-positive prostate cancer, but has undoubtedly contributed to favorable long-term survival in the men in our study," says Bivalacqua.

The next good news is how well the men in this study did. They were treated primarily with surgery alone. Hormonal therapy was delayed until there was clinical evidence of progression, which in most cases was manifested by a positive bone scan. At 15 years after surgery, 7.1 percent of men had an undetectable PSA; 35.1 percent had a detectable PSA but no evidence of metastases; and 57.5 percent were alive and had not died of prostate cancer. The strongest predictors of a favorable outcome were the Gleason score on the radical prostatectomy specimen and

**The number of men diagnosed with prostate cancer in their lymph nodes has dropped from as many as 14 percent during the pre-PSA era to a current low of about 1 to 2 percent.**

the percent (not number) of positive lymph nodes (men with 15 percent or fewer positive lymph nodes did better). In summary, this study shows that highly selected men with positive lymph nodes at the time of radical prostatectomy can live for many years without metastases or other evidence of cancer.

## Genetic Footprints Show Promise in Personalized Management of Advanced Cancer

What is methylation? It's a word that has been popping up for several years now in discussions of prostate cancer. In basic terms, it means that a gene's physical shape changes – think of a LEGO with an extra nub that doesn't fit where it used to, or a lock that no longer works with its key. When this happens to a gene, this is what scientists call an "epigenetic" change; as its shape changes, so does its ability to function. Genes that are supposed to protect the body against enemy invaders are suddenly silenced, for example, and don't put up a defense against cancer.

But these changes, called epigenetic marks, are also like tiny footprints, and as such, they can be very useful for scientists who know how to look for them: Track the methylation, and you'll find the cancer cells, too; currently, biomarkers to detect methylated genes in biopsied prostate tissue and even urine specimens are being developed. Understanding and being able to pinpoint methylated genes may also become a diagnostic tool to help physicians predict the aggressiveness of a man's cancer. Also, scientists believe, this presents a promising new potential target of therapy – a way to get at cancer that has spread beyond the prostate.

As part of an interdisciplinary team, cancer researcher Vasan Yegnasubramanian, M.D., Ph.D., and colleagues in his lab have mapped out DNA methylation on a genome-wide scale in the worst, most aggressive forms of prostate cancer. "For this research, we used multiple lethal metastatic prostate cancers from each of several men who died of their prostate cancer," Yegnasubramanian says. "Our analysis has revealed that although the epigenetic alterations in lethal metastatic prostate cancer are highly diverse across individuals, they are strikingly maintained across *all of the metastases* within each individual."

Yegnasubramanian believes that this work has exciting implications: "This discovery

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highlights the importance and promise of personalized medicine strategies for management of advanced prostate cancer," he says. "Our research team plans to exploit this new understanding of the epigenetic architecture of the lethal metastatic prostate cancer genome to develop new biomarkers for prostate cancer risk stratification and new therapies targeting these epigenetic alterations as part of a personalized medicine approach.

This work was supported in part by the Patrick C. Walsh Research Fund.

## Is it a Gleason 3+4 or 4+3?

If you just do the math, the sum is the same – 7. But there is a significant difference between a prostate cancer determined by a pathologist to be Gleason 3 + 4, which has more lower-grade cells in it, and one that is labeled Gleason grade 4 + 3. Prostate cancer cells are graded on a formula system developed years ago by a pathologist named Gleason. He identified and numbered patterns of prostate cancer in grades of aggressiveness by determining which types of cells appear most commonly in a biopsy sample (and later, in the removed prostate specimen). Cancer given the highest Gleason grade – 8, 9, and 10 – is the most aggressive and in need of treatment. Gleason 7 cancer is different, depending on whether there are more cells labeled 3 or 4.

"The difference between these two patterns can be the need to treat," says Robert Veltri, Ph.D., Director of the Fisher Family Laboratory. One problem is that this determination is often made in a subjective way, depending on which glandular tissue architecture and cell type that appears most often in biopsy samples, and later, in the removed prostate specimen.

In recent work, Veltri and colleagues investigated two new computer-assisted imaging applications to see whether they can be more accurate than the human eye in determining the potential danger of prostate cancer cells. These highly sophisticated programs looked at architectural features

**In recent work, Veltri and colleagues investigated two new computer-assisted imaging applications to see whether they can be more accurate than the human eye in determining the potential danger of prostate cancer cells.**

like the shape of the cells' nucleus, and tissue gland texture to identify Gleason grades 3 and 4. The results were promising. "In our future research, we hope we will be able to use these approaches to predict outcomes such as biochemical recurrence and progression to metastasis," says Veltri.

In other news, Veltri was recognized as the *Journal of Urology's* "Outstanding Reviewer for Basic Science."

## Walsh Honored by American Academy of Arts and Sciences

Patrick C. Walsh, M.D., the University Distinguished Service Professor of Urology, has been honored by the American Academy of Arts and Sciences as the 2012 recipient of its prestigious Francis Amory Prize. Given by the Academy, which was founded in 1780 and is one of the oldest and most prestigious honorary societies in the United States, the prize recognizes major advances in reproductive biology and medical care.

At a ceremony held at the Academy's headquarters in Cambridge, Mass., the Academy presented the Amory Prize to Walsh with a citation that read: "Society has benefited from your path-breaking work as a surgeon, researcher, and teacher. You have forever changed our fundamental understanding and treatment of prostate cancer. For three decades you directed the Brady Urological Institute, whose laboratories,

clinics, and operating rooms produced many of the most important advances in urology and trained thousands of doctors from here and abroad. The anatomic approach to radical prostatectomy that you developed has allowed far more men with early-stage disease to lead normal lives.

"Your characterization of the familial and genetic factors responsible for prostate cancer has broadened our understanding of the disease. You and your colleagues identified the first genetic mutation associated with inherited prostate cancer. Moreover, you have established the largest registry of men with hereditary prostate cancer, and led efforts for improved national standards for the early diagnosis and staging of the cancer.

A member of the Institute of Medicine and editorial board member of *The New England Journal of Medicine*, you have shared your knowledge both in professional journals and in books for the general public. The advances you have made in understanding and treating prostate cancer have galvanized



*Walsh receives Francis Amory Prize for having "forever changed our fundamental understanding and treatment of prostate cancer."*

research and revolutionized the field.

"You have performed 4,569 life-saving surgeries, and with the same commitment and laser-like focus on men's health, you continue to be a source of healing and hope. Distinguished physician-scientist, skilled surgeon, inspired teacher, and relentless investigator, the American Academy of Arts and Sciences is proud to confer upon you the 2012 Francis Amory Prize."

## Brady Investigators Help Gain FDA approval for Two New Tests for Prostate Cancer

For all the good PSA has done, and all the lives it has saved by allowing prostate cancer to be diagnosed years earlier than it would be if men had to rely on a rectal exam alone, this simple blood test has plenty of detractors. Most vocal among them are on the panel (which did not include a single urologist) that made up the United States Preventive Task Force, which recently recommended against PSA screening for prostate cancer. The Task Force also called for more research into finding another biomarker.

Thanks to Brady investigators, there are two more such tests soon to be on the market. Prostate Health Index (phi), a blood test, and PCA3, a urine test, "have been under development for nearly a decade and recently achieved the coveted nod from the Food and Drug Administration for approval," says Alan Partin, M.D., Ph.D., Director of the Brady Urological Institute. Partin and investigators Lori Sokoll, Daniel Chan, Robin Gurganus, and Leslie Mangold, along with other Brady urologists, clinical chemists, nurses, and lab technicians, took part in multi-institutional clinical trials for both tests.

"Our Brady Biomarker Team was responsible for collection and analysis of more than 500 of the nearly 1,600 men who enrolled into these two FDA trials," says Partin. The results of both were positive, "and this means that both phi and PCA3 did a better job of predicting prostate cancer than the PSA test alone. Phi best predicted the presence of prostate cancer among men who had never undergone a biopsy, and PCA3 provided excellent 'negative predictive' value among men who had previously undergone a biopsy, but continued to have a risk for cancer. We should very soon see these markers available commercially."

## Can an Antifungal Drug Work on Advanced Prostate Cancer?

Several years ago, scientist Jun Liu, Ph.D., had a brilliant idea: Because it can take years and many thousands of dollars to develop a new cancer drug from scratch, why not take a second look at drugs that have already been approved by the FDA? Maybe some of them could work against cancer, too. Already, this work is paying off.

During an investigation of a well-known antifungal drug, itraconazole, Liu made two unexpected discoveries. First, he found that itraconazole is capable of blocking the formation of microscopic tumor blood vessels, a process known as angiogenesis. Second, itraconazole also blocks an important pathway called Hedgehog, a series of chemical messaging that occurs normally in the developing embryo that can be hijacked by cancer cells to promote their growth and metastasis.

Liu's findings generated immediate interest, particularly in oncologist Emmanuel Antonarakis, M.D. Because both angiogenesis and Hedgehog signaling are known to be important for the growth and spread of prostate cancer – and because men with advanced prostate cancer are badly in need of a drug that can control the cancer when hormonal therapy stops working – Antonarakis decided to test itraconazole in men with metastatic prostate cancer that had become "castration-resistant" – no longer responsive to hormonal therapy. Antonarakis and his team of clinical investigators randomly assigned 46 men to receive either 200 mg of oral itraconazole daily or 600 mg of itraconazole daily, on a continuous basis. "Encouragingly, we found that 35 percent of the men receiving low-dose itraconazole had reductions in their PSA levels after starting treatment," Antonarakis reports. The men who got the higher dose of itraconazole did even better: "We observed PSA reductions in 54 percent of these men."

In addition, the tumor got smaller in 15 percent of the men on low-dose itracon-

azole and in 28% of men on the higher dose. "Intriguingly, 62 percent of all men receiving itraconazole (low-dose and high-dose combined) had reductions in the number of cancer cells traveling in their circulation (called "circulating tumor cells") that were measured using an experimental technique."

After a more detailed analysis, Antonarakis and colleagues confirmed that the best responses were observed in men receiving the high-dose itraconazole. "In fact," he notes, "there was a direct correlation between higher blood levels of this drug and better clinical responses. The team also found that the higher blood levels of itraconazole resulted in stronger suppression of the Hedgehog pathway, which was examined by obtaining skin biopsies from each patient before and after treatment was started. "This finding suggested for the first time that blocking the Hedgehog pathway may be a very fruitful endeavor in men with prostate cancer." (This idea was first proposed in 2005 by David Berman, M.D., Ph.D. and Philip Beachy, Ph.D., who discovered the critical role of Hedgehog signaling while studying mice with prostate cancer. Discovery has covered Berman and Beachy's ongoing research in previous issues.)

Very encouraged by these results, Antonarakis and colleagues plan to test high-dose itraconazole in men with less advanced prostate cancer. Their next study, expected to begin in the next few months, will focus on patients whose PSA has returned after prostatectomy who have not yet received hormonal therapy. They expect that the clinical benefit of itraconazole in these patients may be even more pronounced. Their ultimate goal is to determine whether taking itraconazole may delay or prevent the development of metastases in these men.



## THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND

# Read About the Research You Have Helped Make Possible

Since 2005, The Patrick C. Walsh Prostate Cancer Research Fund has extended a welcome invitation to all scientists at Johns Hopkins, in every discipline, to apply for funding if they have a good idea worth pursuing that can help us further our understanding of prostate cancer, and help us find the cure. So far, thanks to the tremendous generosity of our patients and friends, we have raised \$34 million. Applications are reviewed by a scientific advisory board composed of distinguished Hopkins scientists and two lay members, Chris Evensen and Sam Himmelrich. Some of the exciting work of these investigators is described below.

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## 2012 AWARDEES

**Michael Caterina**, M.D., Ph.D.  
*Department of Biological Chemistry*

**Samuel Denmeade**, M.D.  
*The Carolyn and Bill Stutt Scholar  
Departments of Oncology, Pharmacology &  
Molecular Sciences, Urology, Chemical &  
Biomolecular Engineering*

**Alan Friedman**, M.D.,  
*Departments of Oncology and Pediatrics,  
Division of Pediatric Oncology*

**William B. Isaacs**, Ph.D.  
*Dr. and Mrs. Peter S. Bing Scholar  
Departments of Urology and Oncology*

**Marikki Laiho**, M.D., Ph.D.  
*Department of Radiation Oncology,  
Division of Molecular Radiation Sciences*

**Shawn Lupold**, Ph.D.  
*The Nancy and Jim O'Neal Scholar  
Departments of Urology and Oncology*

**Martin Pomper**, M.D., Ph.D.  
*Prostate Cancer Team Scholar  
Departments of Radiology, Pharmacology,  
Oncology, Radiation Oncology, Psychology and  
Environmental Health Sciences in the School of  
Public Health*

**Ronald Rodriguez**, M.D., Ph.D.  
*The Irene and Bernard L. Schwartz Scholar  
Departments of Urology, Medical Oncology,  
Cellular & Molecular Medicine*

**Lori Sokoll**, Ph.D.  
*Prostate Cancer Team Scholar  
Departments of Pathology, Oncology, and Urology*

**Dan Stoianovici**, Ph.D.  
*The Virginia and Warren Schwerin Scholar  
Departments of Urology, Mechanical  
Engineering, and Neurosurgery*

## 2012 AWARDEES, RECEIVING 2ND YEAR OF FUNDING

**Mohamad E. Allaf**, M.D.  
*The Peter Jay Sharp Foundation Scholar  
Departments of Urology, Oncology, and  
Biomedical Engineering*

**Trinity Bivalacqua**, M.D., Ph.D.  
*Prostate Cancer Team Scholar  
Departments of Urology and Oncology*

**Gerald W. Hart**, Ph.D.  
*The Beth W. and A. Ross Myers Scholar  
Department of Biochemistry, Cellular &  
Molecular Biology*

**John T. Isaacs**, Ph.D.  
*The R. Christian B. Evensen Scholar  
Departments of Urology and Oncology*

**Phuoc Tran**, M.D., Ph.D.  
*The Phyllis and Brian L. Harvey Scholar  
Department of Radiation Oncology &  
Molecular Radiation Sciences*

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## Cancer-Targeting Agent May Shine Spotlight on Stray Cancer Cells During Robotic Prostatectomy

In open surgery, an experienced surgeon who has just removed a cancerous prostate can often tell by feel whether there is a safe margin of tissue covering the cancer. Tissue that seems adherent or sticky can be a red flag; so can tissue that feels hard. But in the laparoscopic and robotic forms of prostatectomy, with current techniques the prostate is usually not examined until after the operation. If only there were some way to tell in real time, during surgery, whether any cancer cells have been left behind. Soon, there may be.

Urologist Ron Rodriguez, M.D., Ph.D., *The Irene and Bernard L. Schwartz Scholar*, and radiologist Martin Pomper, M.D., Ph.D., *The William R. Brody Professor of Radiology*, and *Prostate Cancer Team Scholar*, believe the secret to spotting stray cancer cells may lie in an enzyme called PSMA (prostate-specific membrane antigen), which is found on the surface of prostate cancer cells. "All prostate cells make PSMA," explains Rodriguez, "but benign cells don't make very much of it, and what they do make stays predominantly inside the cell. Prostate cancer cells, on the other hand, express PSMA right on the surface, and aggressive prostate cancer cells make even higher amounts of it. This makes it an ideal agent for targeting prostate cancer."

Using a molecule that sticks to PSMA, which they have modified to include a near-infrared fluorescent tag, Rodriguez and Pomper hope to "light up" prostate cancer cells left behind at the edges of the removed tumor during surgery, in time for the surgeon to remove them. "We have specially designed laser light sources and near-infrared detecting cameras," says Pomper, who designed the cancer-targeting molecule, called YC-27.

Before YC-27 can be tested in humans, Rodriguez and Pomper will be leading studies to make sure that the agent is safe and well-tolerated, to determine how much YC-27 is needed to detect the cancer, and to refine the light source and detection equipment.

### "Significant progress in imaging."

In other projects, as well, Pomper's group has made "significant progress in imaging, and eventually therapy, of prostate cancer," Pomper reports. "First, with support originally provided by the Walsh Fund, we have developed the first 18F-labeled imaging agent for positron emission tomography (PET scanning) of PSMA, which will make prostate tumors easier to detect." Currently, notes Pomper, PET scanning is not used as much as it could be as a means of detecting prostate cancer, or of staging cancer when it is diagnosed. But in a recent small clinical trial, this new PSMA-targeting agent has proven able to show cancers that have not

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## THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND

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been detected by bone scans or computed tomography (CT scans). “A second-generation agent has shown even higher specificity in preclinical models of prostate cancer,” Pomper continues, “and it will also soon enter the clinic.”

Another project in Pomper’s lab uses a clinically approved nanoparticle that finds cancer cells after they have left the prostate. Doctors have long sought a means of telling where cancer has spread, and the potential – of not only finding small bits of cancer in the body, but of treating them with the same cell-targeting technology – is vast. “This is an extension of work we published involving other cancers last year in *Nature Medicine*,” says Pomper, “and represents the basis of a major project to be submitted for renewal of the Johns Hopkins Specialized Program of Research Excellence (SPORE) in prostate cancer research.”

### Next Step After the HOXB13 Discovery: A Mouse Model of Familial Prostate Cancer

The exciting discovery (see Page 3) by William Isaacs, Ph.D., and colleagues of a major susceptibility gene for prostate cancer, HOXB13, was Step One. Step Two: A mouse model. “Mouse models have proved invaluable in their ability to provide unprecedented insight into the mechanics of human cancer genes,” says Isaacs. “We hypothesize that when a mutated version of HOXB13 is expressed in the mouse prostate, either by itself or in conjunction with an established prostate oncogene, it will promote or accelerate the development of prostate cancer in mice.

HOXB13 clearly plays a role in starting the genetic chain of events that leads to prostate cancer. How does it work? Which pathways does it use? Can this process somehow be blocked or reversed? Understanding the “how” can lead, Isaacs hopes, to “important downstream implications for diagnosis, treatment and prevention of prostate cancer.”



John Isaacs and Samuel Denmeade: “Molecular grenade” can only be detonated by prostate cancer cells.

### New Drug Causes Cancer Cells to Commit Suicide; Early Results Promising

Wouldn’t it be wonderful if we could somehow trick cancer cells into killing themselves? Scientists Samuel Denmeade, M.D., *The Carolyn and Bill Stutt Scholar*, and John Isaacs, Ph.D., *The R. Christian B. Evensen Scholar* working with Danish researchers, have been working to develop and test an agent that can do just that. Technically, it’s not a drug but a “prodrug” – a compound that is biologically inactive when it goes into the body, but that turns into a drug once it’s metabolized.

### A three-day course of G202 reduced the size of human prostate tumors grown in mice by an average of 50 percent within 30 days.

“This can best be described as a molecular grenade,” says Denmeade, “one that can only be detonated by prostate cancer cells” – because only these cells have the secret code required to pull the pin. That code is a protein called prostate-specific membrane antigen (PSMA), found in prostate cells. When the prodrug reaches a prostate tumor, “the prostate cancer cells themselves cause the prodrug to explode,” notes Isaacs. The result is not only a direct hit on the target, but

on some not-so-innocent bystanders, nearby cells that support the cancer.

The results in mouse studies have been impressive: “Destruction of human prostate cancer tumors, with minimal side effects to normal tissues,” Denmeade says. The prodrug, called G202, has passed another hurdle, initial clinical safety studies, and is now being tested in a multicenter, Hopkins-led clinical trial to determine its effectiveness in men with advanced prostate cancer. So far, 29 men have been treated.

In an article recently published in the journal, *Science Translational Medicine*, Denmeade, Isaacs and colleagues reported that a three-day course of G202 reduced the size of human prostate tumors grown in mice by an average of 50 percent within 30 days. How does this stack up to standard chemotherapy? G202 did better, reducing seven of nine tumors by more than 50 percent in 212 days; in comparison, the chemotherapy drug docetaxel reduced only one out of eight human prostate tumors in mice by more than 50 percent in the same time period. Also exciting: The scientists found that G202 also works on other cancers, producing at least 50-percent regression in animal models of breast cancer, kidney cancer, and bladder cancer. Another trial is being planned to test the drug in patients with prostate cancer and liver cancer.

Longtime readers of this publication and its predecessor, *Prostate Cancer Update*, may remember that nearly two decades ago, on a family vacation in the Mediterranean region, Isaacs picked samples of a local weed called *Thapsia garganica*, because he believed it had potential as an anti-cancer drug. For centuries, a toxin made by this plant, thapsigargin, has been known to be poisonous to animals; in fact, it was known as the “death carrot,” because it would kill camels that ate it.

It took many years, but Isaacs and Denmeade managed to disassemble thapsigargin and modify it to target PSMA. How does G202 kill cancer cells? It blocks a pro-

**Denmeade and Isaacs do not believe it's possible for tumor cells to become resistant to the drug. That would be like the lungs becoming resistant to oxygen.**

tein called the SERCA pump, which regulates a cell's level of calcium. Because all cells need this protein to stay alive, Denmeade and Isaacs do not believe it's possible for tumor cells to become resistant to the drug. That would be like the lungs becoming resistant to oxygen.

Also participating in this research were Anastasia Mhaka, Marc Rosen, Nathaniel Brennen, Susan Dalrymple, Bora Gurel, Angelo De Marzo, and Michael Carducci of Johns Hopkins; Ingrid Dach, Claus Olesen, Jesper Møller, and Poul Nissen of the Danish National Research Foundation and Aarhus University; Craig A. Dionne of GenSpera Inc.; and S. Brøgger Christensen of the University of Copenhagen.

**Why Does Cancer Hardly Ever Start in the Seminal Vesicles?**

It's not unheard of, but it is extremely rare for cancer to develop in the seminal vesicles. And yet, as scientist Don Coffey, Ph.D., wondered years ago, why don't they develop cancer very often? Like the nearby prostate, the seminal vesicles are male reproductive organs; their tissues look similar under the microscope. "This is very puzzling," says Marikki Laiho, M.D., Ph.D., Director of the Division of Molecular Radiation Sciences and a 2012 Patrick C. Walsh Prostate Cancer Research Fund Awardee. "Prostate cancer is the most common malignancy in men, but primary seminal vesicle cancers are so rare that only about 50 cases have been described worldwide."

Adding to the mystery: Cancer that starts elsewhere – in the prostate, for instance – has no trouble spreading to the seminal vesicles. Which means that "they cannot resist (already established) cancer better," notes Laiho, "but that they are inherently different in the ability to prevent primary cancer formation."

Could it be, Laiho recently wanted to know, that seminal vesicle cells are somehow able to protect themselves – far better than prostate cells seem able to – from everyday events that cause genetic damage? To answer this question, she and colleagues used "invaluable material derived from prostate surgeries, prostate and seminal vesicle cells and tissues," and compared how prostate and seminal vesicle tissue responded to damage generated by ionizing radiation.



*Laiho: Seminal vesicles may hold the key for protecting the prostate from cancer.*

**Like ruthlessly efficient riot-control police, the seminal vesicle tissue quelled the disturbance very quickly, and did not pass on genetic damage. But the prostate cancer cells, in effect, caved in and waved the white flag.**

"The results were strikingly different," she notes. The radiation-treated seminal vesicle cells displayed "effective and competent cell cycle arrest." Like ruthlessly efficient riot-control police, they quelled the disturbance very quickly – and did not pass on genetic damage to the next generations of cells. But the prostate cancer cells, in effect, caved in and waved the white flag, putting up no visible resistance. "The prostate cells continued their proliferation unabated," says Laiho. "They failed to activate a key damage-surveillance protein, p53." Laiho believes that this work points to "a fundamental difference between the cell types and strengthens the notion that the capability to respond

and repair DNA damage is vitally important to the health of the cells."

If scientists can unlock the secrets of the seminal vesicles, it may one day be possible to beef up the prostate's ability to protect itself from genetic damage – and this, in turn, may help prevent cancer, or slow down its growth.

**New Way To Find Elusive Cancer Cells Floating in the Bloodstream: The Common Cold Virus?**

What are circulating tumor cells? These cells, known as CTCs, are ghosts, echoes of a distant metastatic tumor that enter the bloodstream every once in a while. They're not necessarily the seeds of a brand new tumor, riding the bloodstream like commuters until they find the right stop for their next franchise. Instead, most CTCs just seem to drift like fallen leaves in a creek, swirling aimlessly in the blood. Eventually, most of them die and are washed away; rarely, a few may go on to establish new metastatic tumors.

Scientists have known about CTCs for more than a century, regarding them as elusive prizes for study. "These cells provide a means for us to study a cancer non-invasively, without the need for surgery or a biopsy," says scientist Shawn Lupold, Ph.D., *The Nancy and Jim O'Neal Scholar*. "The real challenge has been to capture, analyze, and quantify these rare CTCs among the enormous background of blood cells, lymphocytes, dead cells, and debris." But how to find and seize these cellular four-leaf clovers? Lupold and colleague Ron Rodriguez, M.D., Ph.D., *The Irene and Bernard L. Schwartz Scholar*, along with research associate Ping Wu, believe the common cold virus may be able to help.

The scientists have plenty of experience using specially engineered viruses as cancer-seeking missiles, tailoring them to target and kill only prostate cancer cells, or even more specifically, cells that make a particular product, such as prostate-specific membrane antigen (PSMA). Although there are promising assays on the market that can capture CTCs in the blood of people with metastatic breast, colon, or prostate cancer, and use the number of CTCs found to help predict the course of disease, "these assays are still

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struggling to achieve high sensitivity and purity,” says Lupold, “and to provide additional valuable information such as CTC viability, tumor gene expression patterns, and genetic mutations.”

Building on their past work with recombinant viruses, the Brady investigators are looking to build diagnostic agents capable of deciphering whatever information can be gleaned from CTCs. They don't want to kill these cells; they want to learn from them: Imagine using a heat-seeking missile and blowing up the Loch Ness monster,

**They don't want to kill these cells; they want to learn from them. Imagine using a heat-seeking missile and blowing up the Loch Ness monster, instead of spotlighting it, watching it, and solving its mysteries. Oops!**

instead of spotlighting it, watching it, and solving its mysteries. Oops! “What we're doing,” explains Lupold, *The Nancy and Jim O'Neal Scholar*, “is engineering this virus to cause infected cancer cells to secrete a highly detectable, luminescent molecule from a tiny crustacean called *Metridia longa*. This is all accomplished in a blood sample, not the patients themselves, to give us information about CTC levels.” The recombinant virus only “lights up,” or “reports,” if it detects prostate cancer CTCs. The level or intensity of this signal may indicate a larger amount of cancer, or a more aggressive cancer.

“The rationale for this approach is multi-fold,” Lupold adds. “The adenovirus reporters only detect living cells, and the ones they detect should be cancer-specific.” One problem with current CTC assays is that they seem to get distracted by background noise – leukocytes, cell debris and other flotsam in the crowded bloodstream. This new diagnostic study is funded by an idea development award from the Department of Defense.

“Our team of researchers is now optimiz-

ing this assay to determine its sensitivity and specificity. We are also evaluating whether this new approach can detect CTCs in a small series of patients with localized and metastatic prostate cancers,” says Rodriguez.

### A New “Twist” in Fighting Metastasis

When it begins, as cancers go, prostate cancer is not that bad. It's contained within the prostate, and in its early stages, its cells are fairly orderly-looking under the microscope. But metastatic cancer is a different animal. Its cell borders become increasingly ragged and blobby, as the cancer divests itself of the things that once made it a law-abiding citizen. What happens to these cells? What makes them change so much? And here's the million-dollar question: Could it be possible to redeem these cells – to give them a “do-over,” a second chance at good behavior?

This thing that happens – metastasis, when cancer cells migrate from the original tumor site and set up shop at distant sites – is what turns prostate cancer into a deadly disease. “There is a process,” explains radiation oncologist Phuoc Tran, M.D., Ph.D., “called epithelial-mesenchymal transition (EMT).” EMT changes cancer cells, strips them down into efficient killing machines and makes them much more able to pick up and go to new parts of the body. “This process causes cells that are part of tightly bound and well-ordered tissue to behave like cells that are less organized and more motile.” EMT is important in normal development, Tran adds, “but it is hijacked by cancer cells in order to gain functions that are important to their ability to undergo metastasis.” Picture a staid vehicle – maybe a dependable-looking minivan – that suddenly shucks its exterior, and underneath is a menacing roadster, built for speed and looking for trouble. “Cells that have undergone EMT are much better able to go to distant body sites.”

Tran's work is a testament to how far we have come in the fight against prostate cancer. Once, there was metastasis, and we watched it happen, feeling powerless. Then,

**Could it be possible to redeem metastatic cells – to give them a “do-over,” a second chance at good behavior?**



Tran: Metastasis is a process with definable steps, each with the potential to be broken.

we began to understand that metastasis is not one invincible enemy, but a process, with intricate but definable steps. One of these specific steps is EMT. And even this can be broken down into smaller steps – each a potential chink in the armor of metastatic cancer, a possible target for new strategies and weapons. “TWIST1 is an important protein that drives EMT,” says Tran, *The Phyllis and Brian L. Harvey Scholar*. “It changes the way that genes are turned on and off. A major goal of our lab is to better predict and treat men whose tumors are more likely to metastasize by understanding the pathways and mechanisms involved in TWIST1 protein activity.”

Tran and colleagues have shown that TWIST1 is present in “abnormally high amounts” in prostate cancer cells. Further, “these TWIST1 levels increase with the Gleason score, or the aggressiveness of the prostate cancer cells,” he says. In mouse models, they have engineered prostate cancer cells that contain high levels of TWIST1. “We have observed that TWIST1 causes prostate cancer cells to have more metastatic ability, and found important regions of TWIST1 that are responsible for this ability. We are now actively searching for compounds and methods to inhibit TWIST1, with the ultimate goal of improving prostate cancer care.”

**In other work:** With urologist Edward Schaeffer, M.D., Ph.D., Tran is also investigating statin drugs as a means of helping avoid a return of cancer in men with intermediate- to high-grade disease. There is a protein called MYC that is “abnormally present in high amounts” in prostate and other cancers, says Tran. “The MYC protein is a promising target for cancer, but it has proven difficult.” However: Statins, common cholesterol-lowering drugs, are known to inhibit several critical pathways. Studies at Johns Hopkins and elsewhere have shown that men who take statins have a lower risk of developing advanced prostate cancer than other men. “Statin use has also been linked to improved clinical outcomes in men undergoing treatment with radical prostatectomy and definitive radiation therapy,” says Tran.

**Once, there was metastasis, and we watched it happen, feeling powerless. Then, we began to understand that metastasis is not one invincible enemy, but a process, with intricate but definable steps. One of these specific steps is EMT.**

Now, Tran and Schaeffer have found that statins target the MYC protein, and this may help explain their anti-cancer effects. “Compared to other novel agents, statins have the advantage of being FDA-approved drugs,” says Tran. “They have been in widespread clinical use and are known to be safe.” The investigators have recently begun, and are accepting patients for, a new clinical trial looking at statins in men with intermediate-risk, localized prostate cancer. “This trial will allow us to determine whether statins can downregulate the MYC protein within prostate cancer cells,” he says. “The data will allow us to open an intervention trial, using statins in patients after surgery or in combination with radiation.”

For this and other work, Tran has recently received several honors and awards,

including an award for the best poster at the EMT International Association’s 2011 Meeting; a Department of Defense Prostate Cancer Physician Research Training Award; and a Junior Investigator Award from Uniting Against Lung Cancer. Tran was named a Research Scholar of the American Cancer Society, and was named Educator of the Year by the Association of Residents in Radiation Oncology.

### **What Makes a Prostate Cancer Cell Turn Metastatic and Hormone-Resistant? Maybe It’s This Protein**

“Although many men develop prostate cancer, it is difficult to identify the men whose cancer will metastasize and become resistant to hormone therapy,” says Michael Caterina, M.D., Ph.D., a 2012 Patrick C. Walsh Prostate Cancer Research Fund recipient. But now, he believes he has an important new clue: A protein that controls the calcium levels within a cell.

The protein in question is named Transient Receptor Potential Vanilloid 2 (TRPV2). Recently, scientists found that the very worst kinds of prostate cancer cells make more of this protein than other cancer cells. TRPV2 “functions essentially as a selective door that can open and close to allow calcium ions to enter cells,” Caterina explains. Calcium levels inside cells control many processes, including movement and migration, gene expression, and secretion of hormones and enzymes. Now scientists have shown that when they lower the production of TRPV2 in aggressive prostate cancers, “not only can they reduce the flow of calcium into these cells, but they can also reduce the tendency of these cells to migrate.”

Caterina believes that the flow of calcium through TRPV2 might be the trigger for cancer cells to migrate out of the prostate. Their mode of escape? They seem to chew their way out. “In order to escape the prostate, cancer cells must digest a web of proteins that confine them there,” says Caterina. “Here again, TRPV2 might be important, because research shows that prostate cancer cells lacking TRPV2 make fewer protein-digesting enzymes than those

with TRPV2. Given these tantalizing observations, we plan to ask two questions. First, is TRPV2 expression truly greater in those human prostate cancers that are more aggressive?”

To answer this question, Caterina and co-investigator Tamara Lotan, M.D. plan to take advantage of a vast repository of prostate tumor samples from human patients.

**Their mode of escape? They seem to chew their way out. “In order to escape the prostate, cancer cells must digest a web of proteins that confine them there.”**

Using antibodies that detect TRPV2 specifically, “we will ask whether this protein is indeed expressed at the highest levels in those tumors that exhibit a more aggressive nature, and whether the expression level of TRPV2 can be used as a predictor of which patients will fare the worst.”

The second question: “Can we take advantage of mice recently generated in our lab that lack TRPV2?” The investigators hope the mice will help them study in greater detail the contributions of this protein to the onset and progression of prostate cancer. They plan to cross mice lacking TRPV2 with another strain of mice lacking a different protein, called PTEN. “Mice lacking PTEN spontaneously develop prostate cancer at a rate much higher than normal,” Caterina explains. Also, the PTEN protein is known to degrade a chemical that normally activates TRPV2. “We predict that the removal of TRPV2 might slow or reduce

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## THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND

the development of aggressive tumors in the PTEN mutant mice.” One result of this work might be finding new ways to identify men with potentially deadly cancer who need aggressive therapy. Caterina also hopes this work will lead to “development of better therapies that specifically block the ability of prostate cancer cells to escape the prostate and invade other tissues.”

### A New Way to Treat Recurrent Prostate Cancer: More Testosterone?

The idea has been in use since the 1940s: Take away testosterone, which prostate cancer cells need to survive and grow, and the cancer will shrink. “When testosterone in the blood circulation is lowered by surgical castration or by drugs such as Lupron or Zoladex, many of the prostate cancer cells within a patient die off,” explains Samuel Denmeade, M.D., *The Carolyn and Bill Stutt Scholar*. “But some of the cells survive, because they adapt to the new environment of low testosterone,” and eventually prostate cancer continues to grow.

Autopsy studies of men who died from prostate cancer have shown that the cells stopped being resistant to the hormonal therapy because they stopped making the testosterone’s main target – the androgen receptor. But other studies have found that some prostate cancer cells adapt to the low-testosterone environment by making even *more* of the androgen receptor. Denmeade believes that this marked increase in the androgen receptor may be the reason why hormone-depriving therapies stop working.

In laboratory experiments, Denmeade and colleagues found that prostate cancer cells that are not killed by hormonal therapy can paradoxically be killed if they get the opposite treatment: high levels of testosterone. “Based on this, we performed a small pilot clinical trial, in which we learned that men with metastatic castrate-resistant prostate cancer could tolerate high doses of testosterone without worsening of side effects or disease.” Quality of life improved for these men, and some men had “significant therapeutic responses lasting up to a year or more,” Denmeade says. These results

were so promising that Denmeade is planning another clinical study “to test whether rapid alteration between low and high levels of testosterone would produce a beneficial response in men with prostate cancer. We believe that rapid cycling between high and low levels does not allow time for the prostate cancer cells to adapt to the ever-changing environment.”

In this next trial, men with very little or no metastatic disease will receive initial treatment to lower testosterone for six months. Then they will receive three monthly injections of testosterone to raise their blood testosterone to high levels; then they will go back to low hormone levels for three

**Quality of life improved for these men, and some men had “significant therapeutic responses lasting up to a year or more.”**

months. This cycle will be repeated twice.

Denmeade hopes that in addition to killing more cancer cells, this treatment plan will improve quality of life by reducing many of the serious side effects of hormone therapy; these can include weight gain, osteoporosis, loss of muscle strength, loss of libido, fatigue, and mood changes.

### If this Stem Cell Protein is Blocked, Will it Kill Prostate Cancer?

There is a certain pronoun with an alphabetical name, called NF-κB (the funny-looking “κ” is pronounced “Kappa”). NF-κB is commonly active in prostate cancer, especially in stem cells within a tumor. “NF-κB helps a prostate tumor grow by increasing the expression of genes that inhibit cell death,” explains scientist Alan Friedman, M.D., a 2012 recipient of funding from the Patrick C. Walsh Prostate Cancer Research Fund.

This protein is activated through the action of a classic signaling pathway, and several groups are working to determine whether blocking this pathway would help slow cancer growth. But Friedman and col-

league Ido Paz-Priel, M.D., have identified another pathway that also causes NF-κB to start its unwelcome activity. This pathway is controlled by another protein, called C/EBP, and Friedman and Paz-Priel believe that blocking this pathway – either by itself, or with the other pathway – may be effective in preventing the rampant growth of prostate cancer.

“We are working to determine the importance of C/EBP-mediated NF-κB activation for the survival of prostate cancer cells,” says Friedman. In laboratory experiments, they are blocking C/EBP in several prostate cancer cell lines and looking to see “whether this leads to their death.” Another important question, which they hope to answer: Does lowering production of the C/EBP protein make prostate cancer cells easier to kill by chemotherapy, by radiation, or by drugs that inhibit the classic pathway of NF-κB activation? Friedman and Paz-Priel are looking for answers to these questions in prostate cancer cells, and also in prostate cancer stem cells. “Through these experiments, we hope to validate the interaction of C/EBP and NF-κB as an important therapeutic target,” Friedman says. The team also is working to develop drugs designed to disrupt this interaction. “In the long-term, we envision evaluating their ability to contribute to the cure of prostate cancer.”

### Ultrasensitive PSA Tests: Can They Be Helpful After Surgery?

After radical prostatectomy, a man’s levels of PSA in the blood are supposed to be undetectable, and for most men, this is what happens. If, months or years after surgery, PSA becomes detectable – above 0.1 ng/ml – and there are no other signs that the cancer has returned, this is called “biochemical recurrence.” “Clinical laboratories can confidently measure PSA at those levels,” says Lori Sokoll, Ph.D., the *Prostate Cancer Team Scholar*. “However, there are ultrasensitive assays that can detect very minute levels of PSA.” Use of these ultrasensitive tests has been controversial. Some scientists have proposed that with these ultrasensitive PSA assays, men who



have PSA levels below a specific cutoff point shortly after surgery could have extra reassurance that their cancer is gone for good, and that men with PSA levels above this point might be monitored more closely. Other scientists and doctors believe that these lower levels may just make men anxious when they don't need to be.

In a preliminary study, Sokoll, with co-investigators Adam Reese, Daniel Chan, Zhen Zhang, and Alan Partin, used an ultrasensitive assay to measure PSA in men after radical prostatectomy who either had biochemical recurrence or were free of recurrence for at least five years. The ultrasensitive test was able to pick up PSA at higher levels in the recurrence group compared to the men whose cancer did not return. The assay was also able to predict which men would likely be free of biochemical recurrence at five years after surgery.

Next, Sokoll and colleagues are seeking to confirm these results in a larger study and to determine whether another ultrasensitive assay used in the Johns Hopkins Clinical Chemistry Laboratory will have a similar performance. "We hope that this study will help to establish whether there is benefit to using ultrasensitive PSA assays in men after surgery to predict their long-term likelihood of remaining cancer-free."

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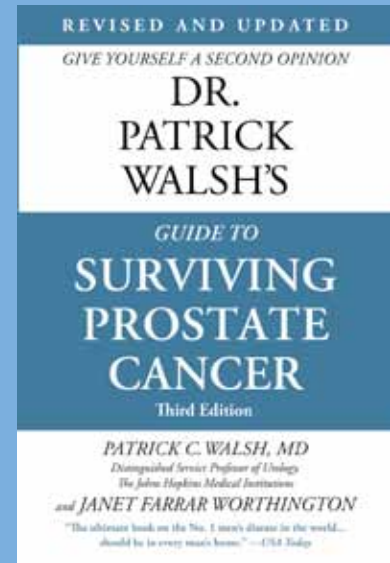
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## “You’ve Got to Give Back”

On the list of worst nightmares, what John and Ginny McDonald were facing must rank at the top. Ginny had been diagnosed with breast cancer, and given just six months to live. Then John found out he had prostate cancer. In his sixties at the time, he went to see urologists at hospitals in his hometown of Philadelphia and didn't like the odds the doctors were quoting for urinary continence and potency. “They gave me an 80 percent chance of having continence but only a 50 percent chance of maintaining potency,” he recalls. “I said, ‘I’m just not ready for that.’ One doctor said, ‘That’s just the way it is.’ There we were, my wife’s fighting breast cancer, I’ve got prostate cancer, my head’s spinning.” Then he read Patrick Walsh’s *Guide to Surviving Prostate Cancer*, and came to Johns Hopkins for a second opinion. He met with urologist Jonathan Jarow, M.D., and instantly “felt I had spoken to a man who knows what he’s talking about.” Jarow (who has left Johns Hopkins to join his wife in Washington, D.C., where he now works for the Food and Drug Administration) told McDonald that his odds of maintaining continence and potency were 80-80. “I said, ‘Sign me up,’” McDonald says. After surgery, Jarow came to visit. “He just didn’t stand there and talk to me, he sat on my bed.

I just felt so comfortable.” McDonald also had peace of mind because the staff at the Brady made arrangements for all of Ginny’s records to be transferred to Johns Hopkins. “So that worry was just taken off of me. If something had happened to her, then Johns Hopkins would have taken care of my wife. I knew she was taken care of, and that left me with only one thing to concentrate on, getting healthy.

Even better, Ginny beat all the odds, and lived for nine and a half more years. “She was one of the ones they call a five-percenter. They last longer than anyone can expect.” Ginny endured grueling treatment at Fox Chase Cancer Center in Philadelphia, then

### “There we were, my wife’s fighting breast cancer, I’ve got prostate cancer, my head’s spinning.”

lived to see her daughter get married, and to see her first grandson. “She saw what she wanted to see in life. She got most of her bucket wishes done.”

The first year past Ginny’s six-month diagnosis – 13 years ago – John McDonald decided to pass on his blessings. “I thought, ‘God’s been good to me, through the knowledge he gave these doctors. I’m going to give to the hospitals for other people to get



John McDonald: Began “Cut for the Cure” 13 years ago to raise money for cancer research.

blessed the way I have been.” McDonald, who owns hair salons, began “Cut for the Cure” in Philadelphia. The money raised goes to support prostate cancer research at Johns Hopkins and breast cancer research at Fox Chase in Philadelphia. Held every October, this event has raised \$22,700 so far for prostate cancer research at the Brady. All gifts to “Cut for the Cure” are tax deductible.

“John McDonald is a wonderful, caring man,” says Brady Director Alan W. Partin, M.D., Ph.D., “whose desire to give back has helped a lot of people.”

McDonald says he tries to achieve balance in his life. “You’ve got to give back. You can’t just keep making withdrawals.”