PROSTATE CANCER
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Out-of-the-box scientific thinkers: Ken Pienta, by the portrait of his mentor, Don Coffey.

Collision Science, Creative Thinking, and Hope for Treating Metastatic Cancer

Meet Our New Research Director: Ken Pienta

Ken Pienta has come home, and it's not to rest on his many laurels, but to challenge himself and the other scientists here at the Brady to find creative new ways to tackle the toughest areas of disease.

In January 2013, Pienta, M.D., succeeded Robert Getzenberg as Director of Research at the Brady – a role held for more than three decades by the legendary Don Coffey, Ph.D. In taking Coffey's old job, Pienta has big shoes to fill, and he knows it well; after earning his M.D. at the Johns Hopkins School of Medicine in 1986, Pienta did his fellowship in medical oncology at the Brady from 1988 to 1991, and Coffey was his mentor. Now, Pienta is the *Donald S. Coffey Professor of Urology* and Professor of Oncology and Pharmacology and Molecular Sciences at the Johns Hopkins University School of Medicine. Like Coffey, the *Catherine Iola and J. Smith Michael Distinguished Professor of Urology*, Pienta was very interested in how the structure and function of cells changed in cancer. After his fellowship, Pienta joined the faculty at the University of Michigan, where he established himself as one of the country's leading researchers of prostate cancer, and was repeatedly named one of America's top doctors for treating it. At Michigan, Pienta was the Director of Precision Medicine for the Michigan Center for Translational Pathology; he also served as Vice President for Research, Health Sciences, and was the Director of the Prostate Specialized Program of Research Excellence (SPORE) in addition to teaching, doing research, and seeing patients. In the midst of all of these responsibilities, Pienta made it a point to maintain an active clinical practice taking care of men with advanced prostate cancer. Why do this? One reason is that scientists tend to get so focused on solving their particular piece of the puzzle that they lose sight of the bigger picture of having cancer – the worry, the fatigue, side effects from medications, what it's like for

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Being the Change We Wish to See

Partin: New tables may help men with PNI

In this issue of *Discovery*, we welcome home Ken Pienta. Ken did his fellowship in medical oncology here at the Brady, and his mentor was Don Coffey, the Director of Research. Now Ken is the *Donald S. Coffey Professor of Urology*, and Professor of Oncology and Pharmacology and Molecular Sciences. He is our new Director of Research, and throughout his career, he has stayed true to what he learned from Don Coffey.

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One of his favorite quotes is from Gandhi: "You must be the change you wish to see in the world." I believe we are all working to do that here.

Two decades ago, our pioneering research on family history highlighted men who were at higher risk for developing prostate cancer, including African American men. Our ongoing work in this area has yielded sobering implications for African American men considering active surveillance. New research, led by urologist Ted Schaeffer, found that compared to Caucasian men, the tumors in African American men are larger, of higher grade, and more likely to appear in harder-to-diagnose areas of the prostate. In other words, African American men need to take a diagnosis of prostate cancer very seriously and seek curative treatment.

In this issue, as always, we do our best to cover every facet of prostate cancer. Length of stay after radical prostatectomy is shorter, and recovery is quicker than ever before. An analysis (see Page 10) of 20 years' worth of radical prostatectomies at Johns Hopkins, led by Phillip Pierorazio and Trinity Bivalacqua, shows a dramatic drop in complications. In recent research, we learned something very important about the finding of perineural invasion (PNI) on a prostate biopsy: Many doctors, as well as patients, don't understand it, and PNI is different for men with low-volume cancer than for other men. Several Brady investigators including Michael Gorin, Bruce Trock, and I have developed a new set of tables (see Page 12) that can help men with this finding choose the treatment that's best for them.

In the area of sexual recovery after radical prostatectomy (see Page 7), research led by Christian Pavlovich and Bruce Trock has found that taking Viagra as needed works better than taking it every night, and Bud Burnett (see Page 10) has good news for men who need help with both urinary continence and erectile dysfunction.

Because the Brady owes its existence to philanthropy, we are always so grateful when our patients want to give back and help support our work. Bob Bruce is one of them (see Page 24). Personally, I am not only grateful, but also very moved that so many of our patients want to help other men and their families with prostate cancer. Thanks to you, we are able to do more for them all the time.

Best wishes,

Alan W. Partin, M.D., Ph.D.
David Hall McConnell Professor and Director
The Brady Urological Institute

Pienta [continued from page 1]

patients and their families to deal with a major illness. "Keeping the patients front and center is a constant reminder of why we're doing this," he says, "why it's so important that we find better ways to treat cancer."

Collision Science

Pienta's website (kenpienta.com) features this quote from Mahatma Gandhi: "You must be the change you wish to see in the world." He is the author of more than 350 journal articles and has been the lead investigator of many clinical trials; he has twice received the American Cancer Society's Clinical Research Professor Award. But throughout his career, Pienta has tried to avoid ever becoming the stereotypical ivory tower academic type, jealously hoarding his research until the next peer-reviewed publication comes out. Early on, Don Coffey taught him to be generous with what he learned. "He always said to make sure to disseminate what you know, and not to worry about being scooped," says Pienta. "I have always tried to stay true to Don's philosophy. At Michigan, when we collected prostate tissue through our tissue acquisition program we gave samples freely throughout the world whenever researchers asked. Over the years, that eventually led to many scientific discoveries." This way of thinking also led Pienta toward what he calls "collision science" – basically, "taking folks from disparate disciplines and getting them to work together at solving problems in the field we are interested in." Although Pienta's own specialty is in treating and studying prostate cancer, "one of my closest research collaborators is a dentist." Why? Dentists are bone biologists, Pienta explains, and that's where advanced prostate cancer tends to spread – the bone.

Pienta has also studied "cooperation theory," as it applies to cancer research, with a professor in the School of Public Policy at Michigan. This collaboration has led to a half-dozen projects Pienta has ongoing with biomedical engineers. "We are trying to create little gadgets that will help us get cells out of the blood." As Director of Research at the Brady, Pienta is fostering an environment where this kind of out-of-the-box thinking and multidisciplinary collaboration can thrive. It has to, he says. "So many of the researchers who trained at the Brady over the years are now directing or working at top-notch programs at other institutions. This creates strong competition, which is good. If we want to remain number one, we have to be the best by continuing to make new and important discoveries and working even harder." Pienta, who was named Distinguished Mentor of the Year in 2009 by the American Urological Association, believes that his role is to understand "what everyone's goals are and then figuring out how best to help each one achieve them."

Scientists tend to get so focused on solving their particular piece of the puzzle that they lose sight of the bigger picture of having cancer – the worry, the fatigue, side effects from medications, what it's like for patients and their families to deal with a major illness.

Cancer Ecosystems

Pienta's own research centers around what he calls "ecosystems" in metastatic cancer. "One of the reasons I came back to the Brady is to accelerate the pace of my own discoveries and come up with an effective ecological therapy that will modify the environment where the cancer cells are found." Most American men who are diagnosed with prostate cancer are cured by surgery or radiation, he notes, "but unfortunately, about 30,000 men still die of metastatic disease in this country every year. Many new drugs for metastatic prostate cancer have been approved in the last three years, but right now, we can't cure metastatic prostate cancer," and the reason may be that the drugs target the wrong aspects of cancer. "The majority of these therapies attack mutations in the cancer cells." But Pienta has come to believe that tumors can be viewed as ecosystems "where the cancer cells are intimately interacting with a variety of normal cells." In this microenvironment of a tumor within the body, he adds, it's the plain old regular cells that help the cancer grow and spread. The interaction of these

cancerous and normal cells actually remodels the microenvironment. "Think of it as an evolving ecosystem," he explains. "We are using this model to design new treatments for metastatic prostate cancer," developing combination drugs that directly target the cancer cells and also attack the microenvironment. "For example, we discovered that almost half of cells in metastatic cancer sites are 'tumor associated macrophages' – cells that should not even be there and have been attracted there to try and clean up the damage being done to the normal tissue by the cancer." Once these cells have been lured to the cancer site, they are co-opted – impressed, like the Shanghaied sailors of old – by the cancer cells to help the tumor grow. "We have already conducted two trials to block these macrophages as a way to treat prostate cancer and are working on multiple new therapies. We refer to this as ecological therapy for cancer."

Pienta is excited about the promise of these multi-targeting drugs. "There is great potential for us to make an exponential leap if we solve issues of drug combinations and figure out how to use targeted therapy correctly. I believe we will discover many innovative treatments, and transition them all the way from the bench to the bedside."

Some material for this story came from an interview with Pienta by Gerald Couzens.

For African American Men, Active Surveillance May Be Risky

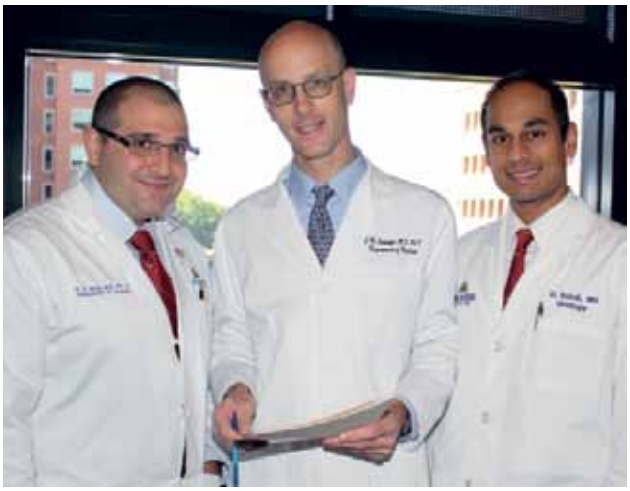
Aggressive Cancer May be Missed

If you are an African American man, you should take prostate cancer very seriously because, unfortunately, your life may depend on it. No other group of men in the world shares your risk of getting prostate cancer, of getting the kind that needs to be treated, of having it diagnosed at a later stage, and of dying from it. Now, important research by Brady investigators has shown that even the "best" kind of prostate cancer – the kind that seems to be very low-risk, the kind that could be treated with active surveillance – may not be as benign in African American men.

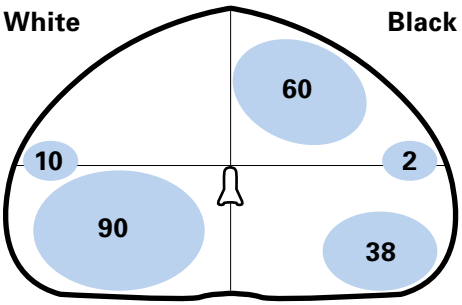
"Active surveillance is a highly successful management strategy for men with very low-risk prostate cancer," says urologist Edward Schaeffer M.D., Ph.D. "But African American men are more likely to be diagnosed with, and die from, prostate cancer." And so, Schaeffer has been wondering, "is conservative management of prostate cancer in African American men a wise choice?"

To find out, Schaeffer, along with colleagues including H. Ballentine Carter, Debasish Sundi, and Ashley Ross, recently studied 1,801 men who met the National Comprehensive Cancer Network's criteria for very low-risk prostate cancer. These men were candidates for active surveillance but elected to undergo immediate prostatectomy instead. The groups consisted of 256 African American men, 1,473 white men, and 72 men of other races. The team investigated pathologic and cancer-specific outcomes in these men, and the results were striking: "Surprisingly," says Schaeffer, "African American men had threefold higher rates of more advanced, aggressive disease, which resulted in much poorer outcomes, compared to white men." In other words, even though these men had been considered at very low risk, their cancer turned out to be more aggressive and more extensive than the initial biopsy and physical exam had suggested.

Barely a tenth of the men in most active surveillance programs are black, although the results are generalized as applying to all men equally. But prostate cancer, even the "very low risk" kind, is different in African American men.



Ross, Schaeffer, and Sundi: In this study, "African American men had threefold higher rates of more advanced, aggressive disease," although their cancer seemed at first to be low-risk.



High-grade cancers tend to form in different areas of the prostate in white and black men: Nearly 60 percent of high-grade cancers in black men were at the top of the prostate – farthest away from the rectum, and hardest to reach in a needle biopsy.

This work, published in the *Journal of Clinical Oncology*, prompted Schaeffer to team up with renowned prostate pathologist Jonathan Epstein for further investigation. In studying the prostatectomy specimens from these men, Epstein found that, compared to Caucasian men, the tumors in African American men were larger, of higher grade, and more likely to appear in harder-to-diagnose areas of the prostate. These findings, published in the *Journal of Urology*, showed

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that African American men had high-grade cancers at the top of the prostate – an area that is farthest from the rectum – nearly 60 percent of the time (see figure). "This is an area of the prostate that is particularly difficult to reach with standard biopsy approaches," says Sundi, the lead author on the studies, "and this may explain why the more aggressive cancers were missed more often in black men." It may be, Schaeffer adds, "that adding special biopsy procedures or prostate imaging with MRI could help identify these more aggressive anterior tumors. This work also suggests that there may be biologic differences in the prostates of African American men that drive these tumors to develop in a different location, and this will be a key area of our research in the future."

Back to Schaeffer's original question: Is active surveillance safe for African American men? Given these results, probably not. "The favorable outcomes achieved for men in active surveillance are based on studies that under-represent African American men." In fact, barely a tenth of the men in most active surveillance programs are black, yet the results are generalized as applying to all men equally. Because "very low-risk" cancers in African American men seem different from those in other men, Schaeffer believes that "we need race-specific recommendations" for the treatment of very-low risk cancer. "African American men need to understand these risks when they choose treatment for their prostate cancer. Specifically, they need to know that if they decide on active surveillance, aggressive cancer may be missed."

HOXB13: Indeed a Major Susceptibility Gene for Prostate Cancer

Some people are born with the tendency to develop cancer. For example, a woman's risk for breast cancer is greatly increased when she inherits a damaged copy of the genes, BRCA1 or BRCA2. And now we know, thanks to the work of William Isaacs, Ph.D., and colleagues, that when a man inherits a mutated form of a gene called HOXB13 (which is important in normal prostate development), his chances of developing prostate cancer are greatly increased.

Why are these men more likely to die from prostate cancer? One reason may be the early onset; the disease may be at its most curable when men are in their forties, long before most men start thinking about prostate cancer.

Doctors and scientists have known for many years that prostate cancer runs in some families, and that for men in these families, prostate cancer seems to develop sooner than it does in other men. But "uncovering the molecular basis for an inherited form of this disease has been challenging," says Isaacs, *the William Thomas Gerrard, Mario Anthony Duhon and Jennifer and John Chalsty Professor of Urology*. Last year, in a genetic study of families with prostate cancer, Isaacs and colleagues at the University of Michigan identified a rare mutation of HOXB13, called G84E, is present in men with a family history of prostate cancer who develop the disease at a younger age. Since those findings were published, nine independent studies have confirmed that HOXB13 is a prostate cancer susceptibility gene. Studies from the International Consortium for Prostate Cancer Genetics, the largest collection of hereditary prostate cancer families in the world, and separate analyses of individual study populations, all have reported that men who inherit the G84E form of the gene have a higher likelihood of developing prostate cancer, with increases in risk ranging from four- to 16-fold.

"The G84E version is most common in the populations of Northern Europe and the Nordic countries – areas that have some of the highest rates of deaths from prostate cancer worldwide," notes Isaacs. Why are these men more likely to die from prostate cancer? One reason may be the early onset; the disease may be at its most curable when men are in their forties, long before most men start thinking about prostate cancer.

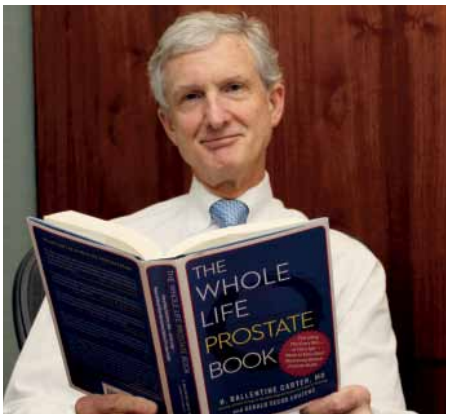
Additional genetic analyses revealed that all of those carrying this mutation shared a "common founder origin" – that is, they share a common ancestor. In Sweden and Finland, about one in 10 men with early onset, familial prostate cancer carries the G84E mutation. Interestingly, a different recurrent mutation in the HOXB13 gene, called G135E, is linked to a higher prostate cancer risk in Chinese men.

"All of these studies clearly show that for prostate cancer, similar to BRCA1 and -2 for breast cancer, HOXB13 is a consistent and strong risk factor," says Isaacs. "These confirming studies emphasize the need for further research so that we can understand the mechanisms responsible for this inherited risk, and begin to translate this information to the clinic."

With support from the Patrick C. Walsh Prostate Cancer Research Fund, Isaacs, who is the *Dr. and Mrs. Peter S. Bing Scholar*, is using DNA sequencing technology to determine whether there are any other mutated forms of the HOXB13 gene. He is also looking for mutations of other genes in the same neighborhood – genes called PRAC and PRAC2 – to see whether they lead to a higher risk of prostate cancer. "We are looking for these mutations in men of European descent, as well as in the understudied, high-risk population of men of African descent," Isaacs explains. "We hope that identifying and characterizing these mutated genes will help us understand why some men develop prostate cancer. We also hope that our findings will lead to new tests to identify these men at higher risk, as well as for potentially new ways to treat or maybe even prevent prostate cancer."

The PSA Screening Debate and Active Surveillance

When the American Urological Association convened a panel to help men and their doctors make decisions about prostate cancer screening, it chose to lead it the Hopkins urologist whose ongoing, pioneering work on PSA screening has shaped much of the



Carter: "There is a lot of confusion because there are so many opinions." Carter is also the author of The Whole Life Prostate Book.

"The major harm of screening is that a substantial minority of men, depending on age, will be diagnosed with a cancer that would never have caused harm. But who can safely avoid treatment?"

debate: H. Ballentine Carter, M.D.

"There is a lot of confusion because there are so many opinions," says Carter. "Views on PSA-based screening for prostate cancer vary widely – from a 'one-size-fits-all' approach that recommends starting when men turn 40, to a recommendation not to use the test at all." Opinions on treating prostate cancer are no less disparate, ranging from "treating all cancers to treating hardly any of them," Carter adds.

The panel's interpretation of the evidence was that men between the ages of 55 and 69 are those most likely to benefit from screening, and that a man should only be screened after hearing about both the benefits and harms. "The major harm of screening is that a substantial minority of men, depending on age, will be diagnosed with a cancer that would never have caused harm," says Carter. "If treated, these men risk the side effects of treatment without the benefit in terms of extending life."

The other approach is not to treat every man diagnosed with prostate cancer. "But who can safely avoid treatment?" Carter began working to answer this treatment 16 years ago when he developed the Active Surveillance Program for prostate cancer at Hopkins. Now the careful collection of data from men in the program is paying off: In 2012 and 2013, a number of studies based on the Johns Hopkins experience with surveillance and surgery were carried out to learn more about the safety of surveillance. The big question these studies sought to answer: Which men can avoid treatment without compromising their chance of a cure?

Investigators from Hopkins, the Fred Hutchinson Cancer Center, and the University of California-San Francisco (UCSF) teamed up to compare the outcomes of men enrolled in the Active Surveillance Program at Hopkins with those of men who underwent surgery immediately at Hopkins and UCSF after their cancer was diagnosed. "Since no trial has directly compared surgery versus surveillance, the investigators used a simulation model to project the likelihood of prostate cancer death in the two groups," Carter reports. The scientists projected that 2.8 percent of men on active surveillance and 1.6 percent of the men who underwent immediate radical prostatectomy would die of their disease in 20 years. They estimated that the average increase in life expectancy associated with immediate radical prostatectomy was 1.8 months, and that men on active surveillance would remain free of treatment for an additional 6.4 years as compared to men who had immediate treatment. "These findings suggest that men enrolled in the Johns Hopkins Active Surveillance Program are at low risk of losing a window of opportunity for cure if they are carefully monitored," Carter says.

However, men who qualify for the Active Surveillance Program are somewhat of an exclusive group; most men who are diagnosed with prostate cancer do not fit the program's stringent criteria. To be enrolled in the Active Surveillance Program at Hopkins, a man must have low-grade and small-volume disease – cancer categorized as "very low risk" (see box).

What about men with low-risk cancer? These men have low-grade, but not low-volume cancers. Recently, Jeff Tosoian, M.D., now a urology resident, studied men with very low-risk and low-risk disease who underwent surgery at Hopkins. "Since they underwent surgery, it was possible to compare the extent of cancer in the two groups," says Carter. After evaluating the extent of cancer among 7,333 men classified as low-risk, and 153 men diagnosed with very low-risk disease, Tosoian concluded that men with low-risk disease were approximately two times more likely than very low-risk men to have a cancer that turned out to be of higher grade and/or to have spread beyond the prostate gland. "This finding suggests that surveillance may be more risky in the presence of low-risk versus very low-risk disease, especially in younger men," says Carter. "Men who can expect to live at least 20 more years who have low-risk disease may rather accept the risks of treatment than take the chance that their cancer will cause harm later, especially if they are otherwise healthy. Men with very low-risk disease can take comfort that their disease can safely be managed by surveillance."

An interesting note: Some men enrolled in active surveillance are found to have a higher grade of cancer in a follow-up biopsy months

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Very Low Risk

You are considered to have *very low-risk* prostate cancer if:

- Your biopsy has a Gleason score of 6,
- 2 cores or fewer are found to contain cancer,
- Cancer makes up half or less of any core that contains cancer,
- PSA divided by the prostate volume is 0.15 or less, and
- Cancer is not palpable on a digital rectal examination

Low Risk

You are considered to have *low-risk* prostate cancer if:

- Your PSA is below 10 ng/ml
- Your biopsy has a Gleason score of 6
- Cancer is not palpable or is minimally palpable on a digital rectal examination

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or years down the road. Does this mean that the low-grade cancer somehow evolved to become a higher-grade cancer? Or did the high-grade cancer just develop by itself? "This is an important question," says Carter, "given the enthusiasm for therapies that target low-grade cancers without destroying the whole gland," treatment known as focal therapy. "In one of our patients on active surveillance, a particularly aggressive cancer was found 16 years after the man was diagnosed with low-grade cancer." Fortunately, the Active Surveillance Program saves the tissue from serial biopsies. Scientist Michael Haffner, M.D., made genetic "fingerprints" of the cancer samples and found that the genetic profile of the aggressive disease was different from that of the low-grade cancer. "This suggests that the higher-grade, aggressive cancer did not arise from the low-grade cancer," says Carter. "It is not known whether this is a unique or a common situation, but in the future we may answer this question using tissue samples stored as part of our Active Surveillance Program."

Testosterone Plus Radiation Equals Better Cancer Control

An unusual observation by Hopkins scientists about how testosterone affects prostate cancer cells may lead to more effective radiation therapy in men with high-risk disease.

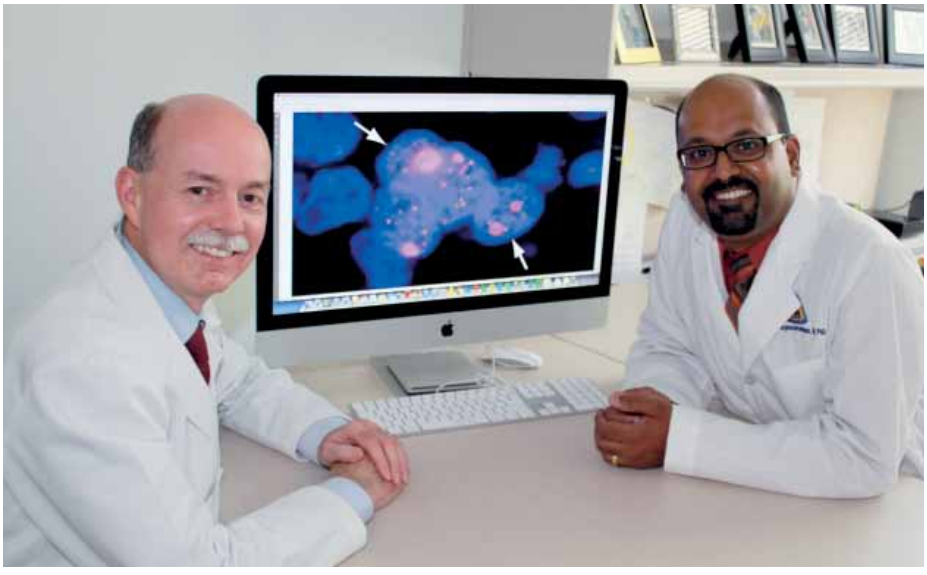
Currently, the standard of care for men with prostate cancer that is likely to recur or spread beyond the prostate is to combine hormonal therapy with radiation therapy – a powerful combined approach that has been shown to improve control of cancer in the pelvis, reduce the likelihood of metastasis, and prolong life. "Typically, we treat men with hormonal therapy for two months, followed by radiation plus hormonal therapy," says Theodore DeWeese, M.D., Chairman of the Department of Radiation Oncology and Molecular Radiation Science. "In some men, the hormonal therapy continues for 24 months after the radiation. Despite this, some 30 to 50 percent of men still have a recurrence of their high-risk cancer. New approaches to improve these outcomes are critically needed."

"We believe our results may have significant implications for altering current clinical management of men with high-risk prostate cancer."

DeWeese, with research scientist Vasan Yegnasubramanian, M.D., Ph.D., and their team, may have found a better way to control the cancer. "Recently, some members of our team found that testosterone stimulation of prostate cancer cells can result in breaks of the DNA," says DeWeese. "This was a novel finding, and in some ways, it's very similar to what we already knew about how radiation also causes breaks in DNA." Putting the two ideas together led DeWeese and Yegnasubramanian to wonder whether they could take advantage of this. Could they coordinate hormonal therapy and radiation in a way that could exploit the DNA breaks, and achieve better results?

"These data led us to consider," DeWeese adds, "that testosterone stimulation after an initial period of testosterone deprivation, when appropriately timed with radiation therapy, might lead to particularly effective control of high-risk prostate cancer – a radical notion that, if proven, would represent a paradigm shift for treatment of high-risk prostate cancer."

DeWeese and Yegnasubramanian began to explore this possibility in the laboratory. First, their team treated human prostate cancer cells growing in a dish with testosterone and radiation. They found that "indeed, the combination of the two treatments resulted in more harmful breaks to the DNA than either one alone." But did the extra DNA damage kill more cancer cells? To answer this question, they treated mice with human prostate tumors "in the same way we treat men with prostate cancer," DeWeese explains. "That is, we first reduced their testosterone level, then delivered radiation to their tumors while the testosterone levels were still low." Just as it does in humans, this treatment helped control the growth of aggressive prostate tumors. But some of the tumors regrew quickly. Next, they tried their alternate timing strategy with testosterone and radiation. "In this experiment, we deprived mice of their testosterone, and once the testosterone was very low, we gave testosterone back to the mice and then irradiated the tumors. As we hypothesized, the mice treated in this way had tumors that were far better controlled



DeWeese and Yegnasubramanian: Giving testosterone after a period of hormonal therapy is "a radical notion that... would represent a paradigm shift for treatment of high-risk prostate cancer."

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than with the standard treatment."

These results suggest that treating prostate tumors with radiation while a jolt of testosterone is simultaneously breaking the cancer's DNA provides better tumor control. "We believe our results may have significant implications for altering current clinical management of men with high-risk prostate cancer," says DeWeese. The next step is to determine the best timing and radiation dosage to get the maximal effect.

Viagra Every Night or Just As Needed?

They are called the "neurovascular bundles of Walsh," and they are the tiny, very fragile bundles of nerves that are responsible for erection. "Ever since Patrick Walsh's discovery of these bundles and his subsequent demonstration of how to spare them during radical prostatectomy, there has been hope for men wishing to regain potency after surgery," says urologist Christian Pavlovich, M.D. "However, even with meticulous nerve-sparing technique, there are still some men whose erectile function does not recover fully after radical prostatectomy." Viagra and similar drugs, known as "phosphodiesterase-5 inhibitors," have helped many men to achieve better erectile function after surgery. But doctors have debated the best way for men to use these drugs: Would it be more helpful for recovery of erectile function for a man to take one of these medications every day, or just as needed?

Two studies of short-acting drugs in this category, Viagra and Levitra, showed conflicting results. One randomized trial found that "nightly Viagra use was beneficial compared to placebo, while a larger trial found that Levitra was most effective when taken on demand, rather than nightly," says Pavlovich. "Nevertheless, many urologists still prescribe taking these drugs nightly after radical prostatectomy, which raises the expense and also increases the potential side effects in men who are recovering from major surgery."

Recently, Pavlovich, Bruce Trock, Ph.D., and colleagues at the Brady decided to address this issue in a study of radical prostatectomy patients under age 65, with good erectile function and supportive sexual partners. They randomly assigned 100 of these men to either nightly or on-demand Viagra (50 mg) for a year after their surgery, followed by one month of taking no medication. "Assessments of erectile function and urinary function were performed during this time, and neither the men nor the physicians knew which group the men had been assigned to," notes Pavlovich. "Placebo pills were given to match the study drug every night or on-demand."

The investigators made several important findings: "First, this study provided more evidence that taking short-acting drugs like Viagra and Levitra every night does not confer any advantages compared to taking them on-demand after radical prostatectomy," Pavlovich says. In fact, erectile function turned out to be similar or better in men who took Viagra as needed, compared to men who took it every night. "We also found that the recovery of both erectile function and urinary function after radical prostatectomy was very much improved by better degrees of nerve-sparing. We also discovered, to our surprise, that urinary quality of life was adversely affected by nightly doses of Viagra in the first months after radical prostatectomy."

What about long-acting phosphodiesterase-5 inhibitors, drugs such as Cialis? These are currently being evaluated in comparable trials, Pavlovich reports. "However, the enthusiasm for daily Cialis use after radical prostatectomy must be tempered by the lack of published data supporting it at this time, by the relaxing effect that Cialis is known to have on lower urinary tract symptoms," which might delay the recovery of urinary continence, "and by the lack of improvement with nightly – compared to on-demand – use of Viagra and Levitra in these studies. Ultimately, it appears that sparing the neurovascular bundles as well as possible, when it's safe to do so, may be the most important thing a surgeon can do to improve a patient's quality of life after surgery." These findings have been accepted for publication in the *British Journal of Urology International*, with a follow-up analysis soon to be published in *Urology*.

Erectile function after nerve-sparing radical prostatectomy turned out to be similar or better in men who took Viagra as needed, compared to men who took Viagra every night.

New Test Can Help Predict Aggressive Cancers

PTEN is a pretty important gene. It's a tumor suppressor, which means that it helps prevent the out-of-control cell growth that can lead to cancer. "It acts like the brakes on a car for cancer cells," says urologic pathologist Angelo De Marzo, M.D., Ph.D., whose laboratory has been studying this gene's loss in prostate cancer for nearly a decade. When PTEN is knocked out – as it is in about half of lethal prostate tumors – cancer cells behave more aggressively. "The loss of PTEN leads to uncontrolled cancer cell growth, and the prevention of cancer cell death. PTEN is one of the few genes whose loss has been consistently associated with aggressive prostate cancer."

"Most studies have found that PTEN loss is a powerful predictor of which prostate tumors are likely to recur or metastasize," says urologic pathologist Tamara Lotan, M.D. In recent animal studies, Charles Bieberich, Ph.D., and his team from the University of Maryland-Baltimore County, working with Hopkins scientists De Marzo, Lotan, and Srinivasan Yegnasubramanian M.D., Ph.D., have discovered that the loss of PTEN in mice enables certain prostate cancer cells that overexpress the MYC oncogene to metastasize and kill the mice.

Measuring the loss of PTEN in prostate cancer tissue has not been terribly easy or effective; for years, pathologists have relied on a slow and relatively more expensive test called "fluorescent in situ hybridization," or FISH, and because the test has been so cumbersome, PTEN loss is not routinely tested when a man is diagnosed with prostate cancer. Thanks to a novel, commercially available antibody that was tested and validated extensively several years ago by De Marzo's laboratory, this may soon change.

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Compared to FISH, the new test is less expensive, faster, and much easier for pathologists to interpret. New studies led by Lotan with De Marzo and others at Hopkins suggest this new PTEN test, based on a relatively simple immunohistochemistry, or IHC, assay, is nearly ready for widespread routine use. In a study of radical prostatectomy patients followed closely for many years by Patrick Walsh, M.D., Lotan evaluated a large number of tissue specimens using a technology called "high throughput Tissue Micro Array." Using the IHC test, she discovered a strong correlation between the loss of PTEN and the signs of aggressive prostate cancer, including the Gleason grade of the tumor as well as the stage of the tumor and the time it took for metastases to develop; this work was published in *Clinical Cancer Research*. In a larger follow-up study published in *Modern Pathology*, Lotan and De Marzo, along with pathologist George Netto, M.D., urologist Misop Han, M.D., and epidemiologist Elizabeth Platz, Sc.D., M.P.H, the IHC test found that PTEN loss correlated with faster recurrences after radical prostatectomy, "again indicating a link between PTEN loss in tumors and aggressive behavior," notes De Marzo.

The new test is less expensive, faster, and much easier for pathologists to interpret.

In another study recently published in *Modern Pathology*, Lotan, along with De Marzo and Jonathan Epstein, the *Rose-Lee and Keith Reinhard Professor in Urologic Pathology*, showed that the PTEN test can help pathologists identify an important subtype of non-invasive tumor called intraductal carcinoma of the prostate. Intraductal cancers spread in ducts within the prostate and don't venture outside the gland, but they keep bad company: "They have been known for years to be associated with highly aggressive and often deadly *invasive* prostate cancers," she says. Intraductal cancers are often difficult for pathologists to diagnose under the microscope, but Lotan has shown that these tumors have almost always lost PTEN, and she believes that this finding may help pathologists "better recognize these tumors and identify men who are at risk for developing metastases and lethal prostate cancer."

Lotan and De Marzo hope the test for PTEN loss will become an important part of the diagnostic arsenal for prostate cancer.

Also using the new IHC assay, De Marzo's lab, helped by Lotan's group, has been able to establish a timetable of what happens in many prostate cancers on the genetic level – key molecular changes that can pinpoint precisely how prostate cancer develops and progresses to become a lethal disease. These results were published in *Prostate Cancer Prostatic Disease*. "We showed that PTEN loss happens after the fusion of two genes, TMPRSS2 and ERG," says De Marzo, "which occurs in about half of all prostate cancers."

With these new insights into prostate cancer's timetable, De Marzo and Lotan hope – now that PTEN loss can be checked more easily and efficiently with the new IHC test – that PTEN will become an important part of the diagnostic arsenal. Say a needle biopsy shows that a man apparently has low-risk disease. Does he need treatment right away? Two studies still in progress may provide definitive evidence. One study relates to work done by epidemiologist Bruce Trock, M.D., and De Marzo's group that found when PTEN loss was present in low-grade prostate cancer, it strongly indicated that higher-grade cancer was nearby. The second study, still under way and led by former Hopkins pathologist David Berman, M.D., Ph.D. (now at Queen's University in Ontario) and Lotan, working with De Marzo and Platz's group, showed that patients whose prostate biopsies showed loss of PTEN were "significantly more likely to harbor tumors at radical prostatectomy that were higher-grade than those without a loss of PTEN," says De Marzo.

In related work, Lotan is heading up the Hopkins effort in a large Department of Defense "Transformative Impact" award, spearheaded out of Memorial Sloan Kettering Cancer Center, to examine whether the PTEN test can help identify men who could benefit from specially targeted drugs to metastatic prostate tumors.

PTEN is one of the few genes whose loss has been consistently associated with aggressive prostate cancer.

"Putting together all of these findings over the last several years," says De Marzo, "it is clear that there is compelling clinical evidence that PTEN loss is associated with aggressive prostate cancer, which is paving the way for the ultimate widespread use of the PTEN IHC test in the clinic for men with low- to intermediate-risk prostate cancer."

Vaccine Therapy for Prostate Cancer: Following the Recipe Is Important

Drake: "Significant anti-tumor effects."

Scientists studying many forms of cancer believe that cancer vaccines – which boost the body's immune system so that it can lead a "home front" strike against cancer cells – hold great promise. GVAX Prostate is a cell-based vaccine, originally developed at Johns Hopkins, that may help the body

target and kill prostate cancer cells. By itself, it is not enough to vanquish metastatic prostate cancer; thus, scientists have been studying ways to combine it with other forms of immune-based therapy to create a multi-pronged attack. Recently, Ipilimumab, a drug that blocks a particular checkpoint in the immune system, called CTLA-4, was approved by the FDA for the treatment of metastatic melanoma. This CTLA-4 blocker (anti-CTLA-4) "has been shown to have powerful anti-cancer effects in some patients with melanoma, and to decrease PSA in some late-stage prostate cancer patients," says Charles Drake, M.D., Ph.D., associate professor of oncology, immunology and urology. "However, it has also been associated with a significant risk of autoimmune toxicity." In addition, the response rate, or how often actual tumor shrinkage occurs, is less than 20 percent even in melanoma. Based on these findings, one way to optimize immune treatment for prostate cancer might be to combine a cancer vaccine like GVAX with a second immune-activating agent like Ipilimumab.

In recent preclinical studies, Drake and colleagues combined CTLA-4 blockade with GVAX and discovered that it's important to follow the recipe: "We found that the order in which the agents are administered is critical, in that anti-CTLA-4 increases vaccine activity only when it's given soon after the GVAX vaccine," Drake says. "When the

The combined approach boosts the immune system in two ways.

proper sequence is followed, one can see significant anti-tumor effects, even at low doses of anti-CTLA4. This could potentially lead to greater efficacy with fewer side effects." This research, supported by the Patrick C. Walsh Prostate Cancer Research Fund, was published in the *Journal of Translational Medicine*. "To our knowledge, this is the first study to report extensively on the importance of timing and dosage in this kind of a treatment regimen."

In other news, Drake and colleagues have developed a mouse model of prostate inflammation that promises to be of great help to scientists studying benign enlargement of the prostate (BPH) and prostatitis. "This could turn out to be a really nice model of chronic inflammatory prostatitis," says Drake. "Some men with inflammatory prostatitis have active inflammation in the absence of infection, which makes us think that it's caused by an autoimmune response. Unfortunately, this group of patients is the most difficult to treat. New insights into this disease process could lead to new ways to treat it, which are desperately needed." This work, by Drake and scientists currently at Yale University, Vanderbilt University Medical Center, University of Pittsburgh Medical Center, and Penn State Mont Alto, was published in *The Prostate*.

Beyond the Freehand Biopsies: A More Precise Approach

Doctors performing a needle biopsy of the prostate do the best they can, but they're the first to tell patients that it's not perfect. Although these biopsies are guided by transrectal ultrasound, they're still "freehand." This means that "the cores are often clustered, they miss regions, and

There are many reasons why needle biopsies miss cancer, including errors in execution – aiming for one part of the prostate but not hitting it.

they do not precisely follow the intended template," says Dan Stoianovici, Ph.D., Director of the Urology Robotics Program. "Biopsy targeting errors are on the order of 9 millimeters – too high to reliably find a clinically significant tumor in the prostate."

There are many reasons why needle biopsies miss cancer, including errors in execution – aiming for one part of the prostate but not hitting it – and problems with the imaging. But Stoianovici believes that one big problem is the lack of a good map – a "general, commonly accepted system to define a prostate location precisely and accurately." Instead, biopsy samples are usually taken from regions of the prostate, "but these are not assigned relative to the prostate, and they are different from one session to another and across imaging modalities and procedures."

In an effort to produce more accurate biopsies, Stoianovici, with urologist

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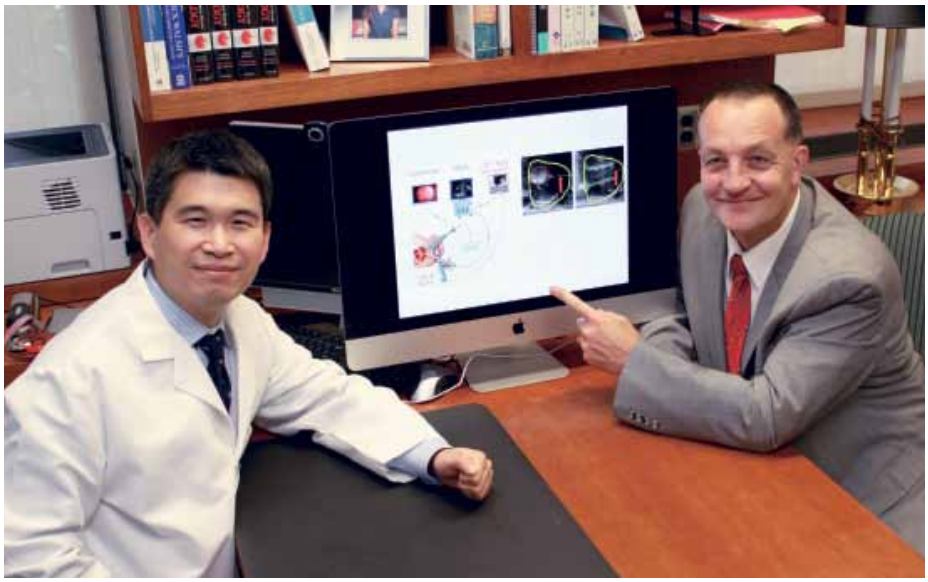

Han and Stoianovici: Making biopsies more accurate with a new Prostate Coordinate System.

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Misop Han, M.D., and postdoctoral fellow Doyoung Chang, Ph.D., has developed a Prostate Coordinate System (PCS), a frame of reference that could be assigned to the prostate of each patient, "with little variability among physicians, over time, and independent of the imaging used." Such a system could be a breakthrough in prostate navigation; imagine the difference to an ocean voyager of sailing to a particular latitude and longitude point instead of using geographic landmarks to find the way.

In a recent study, three urologists and three engineers were trained to use the PCS software and asked to assign the coordinates five times for three patients. The average time it took to assign the coordinate points was just over five minutes, and the results showed that "the PCS can be consistently assigned to the prostate in 3D transrectal ultrasound imaging," says Stoianovici. Further studies are necessary to confirm that the PCS can be consistently assigned using other forms of imaging, such as MRI. This work was supported by the Patrick C. Walsh Prostate Cancer Research Fund.

For Men with BPH, Robot-Guided Vaporization of the Prostate

Although it's called "enlargement of the prostate," the problem in benign prostatic hyperplasia (BPH) is also an overgrowth of tissue *within* the prostate, causing urinary symptoms when the tissue begins to constrict the urethra. One popular, minimally invasive treatment is photoselective vaporization of the prostate, or PVP. But "in spite of its widespread use, there are several limitations in assessing the surgical outcomes of PVP," says urologist Misop Han, M.D. For example, "it is unknown how much prostate tissue is destroyed or left behind after PVP. Instead, the surgery is considered complete when we can see a 'large enough' cavity within the prostate through the cystoscope. This limitation can potentially result in future tissue regrowth and a need for retreatment. It is also difficult to find out where the tissue vaporization occurs in relation to the surrounding structures."

With Dan Stoianovici, Ph.D., Director of the Urology Robotics Program, and doctoral student Chunwoo Kim, Han has developed a new approach to PVP using transrectal ultrasound guidance. The transrectal ultrasound probe is manipulated by a robotic device, developed at the Urology Robotics laboratory.

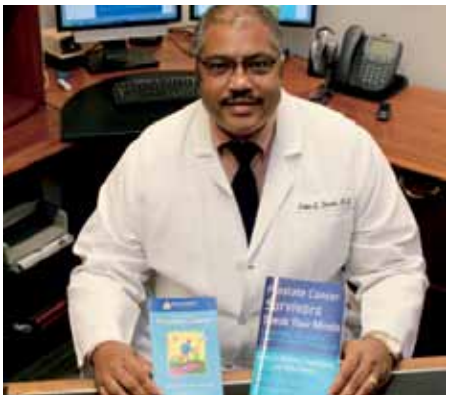
A clinical trial for this new image-guided approach is in progress. "If it is successful," says Han, "this will provide additional means for monitoring the surgery so that we can safely remove a large part of the gland and minimize the need for retreatment."

A Combined Operation to Restore Urinary and Sexual Function

Having both urinary incontinence and impotence after radical prostatectomy should be a rare complication, but some men find themselves in this situation and need help. Surgeon Arthur Burnett, M.D., M.B.A., has good news for these men: A successful operation that restores both urinary continence and potency at the same time.

"The conventional management for men having both erectile dysfunction and urinary incontinence after radical prostatectomy has been separate operations, in which a man undergoes correction of one problem at a time," with implantation of an inflatable penile prosthesis and an artificial urinary sphincter, respectively, says Burnett, the *Patrick C. Walsh Distinguished Professor in Urology*. "These options represent surgical interventions for some of the most severe occurrences of these complications, while achieving high satisfaction rates."

But Burnett has been offering an alternative option, implanting both devices at one surgical setting, for 13 years. "It has the advantage for efficient and rapid resumption of both functions," he notes. Burnett recently reviewed a consecutive series of 55 men who underwent this combined procedure at Johns Hopkins from January 2000 to December 2011. In the study, published in the *Journal of Urology*, he described the specialized surgical technique and showed that the rate of complications with the combined operation was just as low as in men who had two separate operations. "This investigation has confirmed that combination prosthetic device surgery is an option, in additional to single implantation surgery, to enable men sustaining sexual and urinary functional complications after prostate cancer surgery to become functional again."



Burnett, who has written two books for men with prostate cancer, has good news for men who need extra help: A successful operation that restores urinary continence and potency at the same time.

Radical Prostatectomy: Dramatically Lowered Risk of Complications

If this were 1991 and you were about to undergo a radical prostatectomy, you would expect to be in the hospital for at least a

week. Today, you will most likely go home in one to two days. This and other aspects of postoperative recovery in thousands of patients who underwent radical prostatectomy at Johns Hopkins were studied recently in a review of the changing "clinical care pathway" from surgery to discharge from the hospital. The analysis, by Phillip Pierorazio, M.D.; Jeffrey Mullins, M.D.; Ashley Ross, M.D., Ph.D.; Elias Hyams, M.D.; Alan Partin, M.D., Ph.D.; Misop Han, M.D.; Patrick Walsh, M.D.; Edward Schaeffer, M.D., Ph.D.; Christian Pavlovich, M.D.; Mohamad Allaf, M.D.; and Trinity Bivalacqua, M.D., Ph.D.; was published in the *British Journal of Urology*.

Radical prostatectomy in the analysis included the retropubic radical prostatectomy (RRP), known as the "Walsh Procedure," pioneered at Johns Hopkins, and a newer minimally invasive version of this procedure; laparoscopic radical prostatectomy (LRP); and robot-assisted laparoscopic radical prostatectomy (RALRP). (This study did not include men who underwent the perineal procedure and men who had previous reconstructive surgery of the urinary tract.)

"Post-operative clinical care pathways have changed the way we manage many diseases, and radical prostatectomy is a wonderful example."

"The postoperative clinical care pathway after radical prostatectomy has changed dramatically over the past 20 years at Johns Hopkins," says Bivalacqua. The decrease in length of stay has been influenced by factors including "improvements in the knowledge of prostatic anatomy and surgical technique pioneered by Walsh, which have improved blood loss during the operation, decreased the rate of blood transfusion – from between 62 and 89 percent in the 1980s to 0.8 to 3.4 percent most recently – and improved patient convalescence." Other factors include improvements in anesthesia and postoperative pain control; a move driven by both physicians and patients to get out of the hospital sooner; and the difficult economic environment and efforts to decrease costs.

Since 2005, Hopkins has had a one- to two-day clinical care pathway to discharge from the hospital, regardless of surgical approach. It begins with patient-controlled anesthesia, a clear liquid diet, walking the night of the surgery, transitioning to oral pain medications and solid food, and walking a minimum of four times on the day after surgery. All patients are educated about caring for their catheter and what they should expect over the next few weeks by trained nursing staff. For most men, surgical drains are removed before discharge.

Of 18,049 men who underwent radical prostatectomy between 1991 and 2011, nearly 84 percent (15,360) had RRP; nearly 7 percent (1,263) had the LRP; and nearly 8 percent (1,426) chose RALRP. "Interestingly, the average length of stay decreased from 7.7 days in 1991 to 3 days in 1999," says Pierorazio, "and this remained stable until 2004, when the minimally invasive radical prostatectomy emerged here." In 2005, 75 percent of all radical prostatectomies done at Hopkins were RRP; since then, that number has decreased to 60 percent, LRP has remained relatively stable at around 10 percent, and RALRP has increased from 14 percent to 30 percent of all procedures formed.

"In the overwhelming number of cases, an accelerated hospital recovery pathway of one to two days is successful regardless of surgical approach," says Bivalacqua. Only 126 men had a delayed discharge and were considered "off the pathway." The most common reasons for this included bowel obstruction, anemia, blood transfusion or bleeding, blood in the urine, and urine leakage. Most of these complications occurred in the men who underwent RALRP. African-American men also had a slightly higher risk of a longer hospitalization.

"There are two important take-home messages from this analysis," says Pierorazio. "First, post-operative clinical care pathways have changed the way we manage many diseases, and radical prostatectomy is a wonderful example. Second, while RALRP had a slightly higher rate of extended hospital stay, at our hospital fewer than 1 in 50 patients were discharged 'off-pathway.' This may help manage patient expectations following surgery."

Breaking the Chain of Metastasis

If the cells that are found early on, when cancer is confined to the prostate, somehow wanted to leave the home base and establish themselves in distant sites, they couldn't do it. They wouldn't be up to the task of traveling and breaking new ground. "In order for prostate cancer cells to metastasize, a lot of things have to happen," says bioscientist Michael Caterina, M.D., Ph.D. "They must change their shape, escape the prostate, and migrate to other tissues." All of these little challenges, which metastatic cancer cells manage to overcome, are potential targets for treatment – individual links that could disrupt a whole chain of events.

With urologic pathologist Tamara Lotan, M.D., Caterina is studying one potential link in the chain of metastatic prostate cancer, an ion channel protein called TRPV2. First, Caterina and Lotan demonstrated the presence of TRPV2 in three different cell lines of human prostate cancer. Then, using commercial antibodies that recognize TRPV2, "we stained a human prostate sample that contained both normal tissue and a relatively low-grade prostate tumor," says Caterina. "Interestingly, the signal from these antibodies exhibited a greater intensity in the normal prostate cells than in the tumor. Although we cannot yet be certain that it is truly the TRPV2 protein that is being detected, this result suggests that we have much to learn regarding the relationship between TRPV2 and tumor aggressiveness." To find out more, the scientists have begun to cross mice that lack this protein with another line of mice that tend to form aggressive prostate tumors, "so that we can directly evaluate the importance of TRPV2 to tumor progression." Caterina and Lotan also have custom-manufactured antibodies in the lab that recognize both human and mouse TRPV2, "so that we can learn more about whether, and how, TRPV2 contributes to aggressive prostate cancer in mice and in humans." This work was supported by the Patrick C. Walsh Prostate Cancer Research Fund.

New Weapon in Metastatic Cancer: Testosterone

Shutting down the supply of testosterone, through medication or surgical removal of the testicles, has been a standard form of treatment for metastatic prostate cancer ever since 1941, when urologist Charles Huggins discovered that it can dramatically slow the progress of the disease – work that earned him the Nobel Prize. But the beneficial effect of this hormonal therapy on cancer doesn't last forever.

"Over time, all men become resistant to it," says oncologist Samuel Denmeade, M.D. "Further blockade of testosterone by new agents such as abiraterone acetate (Zytiga) or enzalutamide (Xtandi) produces a modest effect in some patients, but resistance to these drugs also develops."

But in a recent clinical study, Denmeade and his team have found that when they give prostate cancer a big shock – high doses of testosterone, after cancer has percolated along for months or years in a very low-testosterone environment – it makes a big difference.

"Surprisingly, many of the men had a drop in PSA levels and a decrease in the size of their tumor sites."

"We gave high doses of testosterone to men with prostate cancer who were progressing on long-term hormonal therapy," he says. "Surprisingly, many of the men in the trial had a drop in PSA levels and a decrease in the size of their tumor sites." The testosterone did not cause any harmful side effects. Instead, "most men experienced an improvement in their quality of life. In some men, sexual function returned." The results of these studies are expected to be published soon. Denmeade is now testing this concept in men with earlier-stage prostate cancer, with alternating three-month cycles of testosterone followed by three months of low testosterone.

Weakening Advanced Prostate Cancer

Barakat: Making cancer more susceptible to chemotherapy

Advanced prostate cancer is difficult to treat because it's resistant to chemotherapy, radiation therapy, and hormonal therapy. "We need a better understanding of the underlying mechanisms in advanced disease," says postdoctoral fellow David Barakat, Ph.D. Working with two oncologists, Alan Friedman, M.D., and Ido Paz-Priel, M.D., he is studying a family of proteins called C/EBPs, which control cell growth. "We previously found that C/EBPs, in cooperation with another protein, block cell death by increasing the expression of certain pro-survival genes," says Barakat.

Now the scientists have shown that one form of this protein, called C/EBP beta, is made in prostate cancer cells – and that when it is suppressed, the cancer is more susceptible to chemotherapy. In laboratory studies, when C/EBP beta is reduced, prostate cancer cells are less able to form new colonies, "further indicating a critical role for C/EBP beta in prostate cancer cell survival." Their work also suggests that C/EBP is increased in men who are undergoing hormonal therapy. "We think that up-regulation of C/EPB beta is a resistance mechanism that allows prostate cancer cells to survive androgen deprivation," says Barakat. It may be that blocking this protein will make hormonal therapy more effective, as well.

When Perineural Invasion Is Found on Prostate Biopsy

What do you do if your prostate biopsy comes back showing perineural invasion (PNI)? Recently, Hopkins scientists have learned something important about this finding: Many doctors, as well as their patients, don't understand it. New tables developed at the Brady may help.

"The finding of PNI on a prostate biopsy has long been felt to be a risk factor for the extension of cancer outside of the prostate gland," says Alan W. Partin, M.D., Ph.D., the *David Hall McConnell Professor in Urology* and Director of the Brady. In fact, one recent meta-analysis found that men who have PNI on a prostate biopsy have about a twofold higher risk of having cancer that has spread beyond the prostate than men who don't have it.

However, low-volume cancer seems to play by different rules. "A study from Johns Hopkins of men with very low-risk prostate cancer – men who were otherwise candidates for active surveillance, but who chose to have surgery – found no association between PNI and the risk of cancer spreading outside the confines of the prostate gland," Partin says. "Taken together, these studies suggest that the urologic community has yet to fully understand the prognostic significance of PNI on a prostate biopsy, especially among men with low-volume disease."

Seeking to help men with this finding who are trying to choose the treatment that's best for them, Partin and colleagues have developed new risk tables. These tables – like the well-known Partin Tables, except focused on PNI – set forth the more exact risk of having cancer that is not confined to the prostate. Using the PSA, clinical T stage, biopsy Gleason score and tumor volume – "the volume is really the key to this work," explains Partin – the tables estimate risks of having non-organ-confined disease. "Using these tables, men and their physicians can now more accurately judge the risk of having cancer located outside of the prostate, thus allowing for more informed decisions about treatment." The analysis was done by Michael Gorin, M.D., Heather Chalfin, M.D., Jonathan Epstein, M.D., Zhaoyong Feng,

Ph.D., Partin, and Bruce Trock, Ph.D. "The study's first author, Michael Gorin, is a junior resident at the Brady, and the second author, Heather Chalfin, just started her internship in urology here at Hopkins," notes Partin.

The Innocent-Looking Seeds of Metastasis

Scientist Michel Haffner, M.D., who studies prostate cancer, is a molecular archeologist. Digging with precision and delicacy, he uncovers layer after layer – creating a timeline of what's happening in individual bits of tumor, so that he can capture the true story of what went wrong.

"In many men, multiple, independent tumor nodules can be identified within a diseased prostate gland," says Haffner. Although just millimeters away from each other inside the same gland, "these individual lesions in the prostate are often genetically different. They also have different structures, and they can contribute to the progression of the disease in different ways."

Why aren't all these little tumors alike? And how are tumors within the prostate related to distant, life-threatening metastases? Haffner is part of a multidisciplinary team working to find out. The team, including Angelo De Marzo, M.D., Ph.D., William Isaacs, Ph.D., William Nelson, M.D., Ph.D., and Srinivasan Yegnasubramanian, M.D., Ph.D., "has started to address the question of genealogy of aggressive prostate cancer in a unique way," says Haffner. Thanks to one patient who agreed to donate tissue at an autopsy that was performed shortly after his death, the team received tissue samples from the primary prostate tumor and also from distant metastases. "We used comprehensive whole-genome sequencing to determine the blueprint of all cancer-associated alterations in the metastases," looking to see which genes were involved, and how they related to the cancer that was found within the prostate gland. When they compared the genetic makeup of the metastatic cells with that of the cancer cells confined to the prostate, "to our great surprise, we found that only a very small and well-differentiated lesion in the primary tumor showed the same set of mutations that were also found in the metastases," says Haffner. "The vast majority of other lesions appeared not to be strongly related to the metastases. This suggests that a small, microscopic lesion in the primary tumor can generate the entire metastatic burden."

How are tumors within the prostate related to distant, life-threatening metastases?

It is troubling to think that one innocent-looking bit of tumor in the prostate – well-differentiated, like the "good" cancers that earn a low Gleason score – could contain the seeds for all the trouble that comes when cancer spreads to distant sites. "This finding highlights the complexity and heterogeneity of prostate cancers," says Haffner, "and stresses the need for new molecular markers that will allow us to determine early on if a lesion shows a high risk for metastasis."

Tweaking the Gleason System: Is there a Better Way to Grade Prostate Cancer?

The Gleason grading system for prostate cancer is at once helpful and confusing for doctors and patients. Part of the confusion is that the Gleason number represents a combination of cell patterns that the pathologist sees in biopsied prostate tissue samples under the microscope. The most common cell pattern and the second-most common pattern are added together, and the sum is the Gleason score. "There are some problems with the Gleason system," says pathologist Jonathan Epstein, M.D., the *Rose-Lee and Keith Reinhard Professor in Urologic Pathology*. Briefly, the Gleason system assigns scores to prostate cancer cells based on how they look, on a scale from 2 to 10. The most normal-looking, slowest-growing cells have the lowest numbers; at the high end of the scale are very malignant cells that are more aggressive and spread quickly. But no man ever gets a score of Gleason 2.

"Patients will be reassured that when they're diagnosed with a Gleason score 6, this means that their Prognostic Grade Group is I out of V, not six out of 10."

"Gleason score 6 is typically the lowest grade assigned," says Epstein, and "patients are unduly concerned when they're told that they have Gleason score 6 cancer, logically but incorrectly assuming that their tumor is in the mid-range of aggressiveness." Gleason score 7 disease can have two meanings: If the most common cell type is Gleason 3, with fewer Gleason 4 cells, this is considered "Gleason score 3+4=7" disease. "In the past, any Gleason pattern 4 tumor was considered aggressive," says Epstein. "But we showed that Gleason score 3+4=7 cancer has a very favorable prognosis, with over 90 percent of men cured after radical prostatectomy." On the other hand, if there are more Gleason 4 and fewer Gleason 3 cells, this is "Gleason score 4+3=7" disease, and it is significantly more aggressive. Gleason scores 8-10 tumors are routinely grouped together, Epstein continues, "but we found that although Gleason score 8 tumors are aggressive, they are not as aggressive as Gleason score 9-10 cancers."

In an article recently published in the *British Journal of Urology*, Epstein and colleagues Phillip M. Pierorazio, Patrick Walsh, and Alan Partin suggested grouping Gleason scores into five prognostic groups, as opposed to the individual nine Gleason scores. "Patients will be reassured," says Epstein, "that when they're diagnosed with a Gleason score 6, this means that their Prognostic Grade Group is I out of V, not six out of 10." Similarly, men with Gleason score 3+4=7 cancer would be placed in Prognostic Grade Group II, "which is in line with their tumor's relatively less aggressive behavior. At the other end of the grade spectrum, men with Gleason score 9-10 tumors will be more accurately considered to have more

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aggressive tumors than those with Gleason score 8, and this can be factored into their treatment decisions."

Good News for Men with Gleason Score 6

In other news, Epstein and colleagues recently took a closer look at the behavior of Gleason score 6 prostate cancer; their findings were published in the *American Journal of Surgical Pathology*. Although Gleason score 6 cancer is considered slow-growing and not aggressive, it has been found – rarely – in studies of prostate specimens after radical prostatectomy, to have spread outside the prostate. Could Gleason 6 cancer ever spread to the pelvic lymph nodes? Good news: The answer is no. "We performed a search of the radical prostatectomy databases at four large academic centers," says Epstein. "In more than 14,000 radical prostatectomies, there was not a single case of a Gleason score 6 tumor ever spreading to lymph nodes." It takes a Gleason score of 7 or higher for prostate cancer to become aggressive enough to spread far beyond the prostate. Under the microscope, Gleason score 6 cells appear uniform, "and they have a more predictable, excellent prognosis," Epstein notes. Gleason score 6 disease has such a good reputation as being "indolent" – slow-growing and well-behaved, as cancers go – among pathologists that some of them have questioned whether it should still be considered cancer. Yes it should, Epstein says. One important reason why is that the biopsy Gleason score is often adjusted after radical prostatectomy, when the prostate is studied by a pathologist, "because the biopsy often underestimates disease grade and extent." Also, "if men think that Gleason 6 tumors are not cancer, this could result in a missed opportunity for cure."

A New Approach

Five Gleason Groups Based on Prognosis

Prognostic Group I:
Gleason score <6,

Prognostic Group II:
Gleason score 3+4=7

Prognostic Group III:
Gleason score 4+3=7

Prognostic Group IV:
Gleason score 8

Prognostic Group V:
Gleason score 9-10

Methylation Changes: "Extra Baggage" on DNA Seems to be Permanent

We all carry extra baggage that we don't want. It turns out that DNA is no different; it accumulates some barnacles, too – tiny changes that don't look like much, but which make a gene unable to function properly. Scientists used to think that these methylation changes were "plastic" – that they weren't necessarily permanent. But a recent study by William Nelson, M.D., Ph.D., the *Marion I. Knott Director* of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, and Vasan Yegnasubramanian, M.D., Ph.D., is changing that viewpoint.

The study, published in *Science Translational Medicine*, revealed for the first time that DNA methylation changes in cancers were like other, more serious alterations – events like mutations, deletions, insertions, translocations, and amplifications. And when they happen as cancer is progressing, they can threaten life. "Of course, essentially all human cancers harbor epigenetic defects," changes to genes that come from an external source, such as diet, "including DNA methylation abnormalities," says Nelson. "And these can be passed on to succeeding generations when cells divide. Nonetheless, we thought that they were reversible in any cell at any time."

To test whether these epigenetic defects in cancer cells go away as the disease progresses, Nelson and Yegnasubramanian invented

DNA accumulates some barnacles – tiny changes that don't look like much, but which make a gene unable to function properly.

a new platform for genome analysis that can simultaneously assess DNA methylation defects and the alterations in next-generation cells in different samples of metastatic cells from men who had died of prostate cancer. "Our logic was that if DNA methylation changes were stable, then similar, if not identical, alterations should be present in each metastatic deposit recovered from any man who had died of prostate cancer." This proved to be the case, leading Nelson and Yegnasubramanian to conclude that DNA methylation changes are equivalent to mutations, and "thus could formally be considered drivers of cancer."

What they have learned, Nelson says, "gives further weight to the ongoing attempts to exploit cancer-specific DNA methylation changes as molecular biomarkers." Knowing what to look for could help scientists develop new tests for prostate cancer screening, early detection, and helping to predict a man's risk of having aggressive cancer. "It also adds promise to the growing arsenal of epigenetic drugs that are slowly working into early-phase clinical trials for cancer."

For Metastatic Prostate Cancer, a Trojan Horse with a Toxic Payload

Metastatic prostate cancer is notoriously difficult to kill. The cells don't divide as quickly as those of other cancer cells, so they can't be felled by chemotherapy drugs that target rapidly growing cancers. Second, by the time prostate cancer has spread far beyond the prostate, only part of it is responsive to hormonal therapy; the rest is unfazed when the male hormones are shut down. Third,

it is very hard to know exactly where metastatic prostate cancer is hiding in the body. Some of it can be seen, if it has established itself in the bone. But a few hard-core cancer cells drifting around in the bloodstream or even in another organ, such as the liver, can remain undetected indefinitely.

Now John Isaacs, Ph.D., and colleagues have developed and validated in preclinical testing a "Trojan horse" that uses stem cells and delivers a toxic payload only to metastatic prostate cancer cells. Based on the foundation of their work, the first clinical tests of this agent are set to begin in men with advanced prostate cancer.

This approach uses a certain type of stem cells, called mesenchymal stem cells. The huge benefit of these particular cells is that they come from healthy adults who donate bone marrow, cause no immune reaction – which means that no immune-suppressing drugs need to be taken and the recipient won't reject them – and they can be cultivated in the laboratory using already-approved methods. "This is an exciting milestone in research," says Isaacs, "because no trial has ever evaluated these cells in any cancer patient, including those with prostate cancer."

This therapy, which will be given intravenously, was developed by a multidisciplinary team of scientists based at several centers, including Isaacs and Samuel Denmeade, of the Chemical Therapeutic Program of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; Neil Bhowmick of the Uro-Oncology Research Program of the Samuel Oschin Comprehensive Cancer Institute at the Cedars-Sinai Medical Center; Jeffrey Karp, Co-Director of Regenerative Therapeutics at the Brigham and Woman's Hospital at Harvard; and Alan Partin and Trinity Bivalacqua at the Brady Urological Institute. The group has been awarded a two-year Challenge Award from the Movember Foundation/Prostate Cancer Foundation to begin the clinical trial, which will be led by Denmeade, Partin, and Bivalacqua. In other preclinical tests, Bhowmick, Denmeade and Isaacs are also investigating cancer-killing microparticles, to be loaded into the stem cells, and will select the most promising microparticles for future clinical development. These studies are supported by a Department of Defense Synergistic Idea Award, for which Isaacs is the principal investigator.

Will this Drug Work on Advanced Cancer?

One of the most challenging aspects of treating advanced prostate cancer is that – because each case of prostate cancer is unique – not every drug is effective in every man. Enzalutamide is a prime example: Approved in 2012 by the Food and Drug Administration for certain men with advanced prostate cancer, it targets the androgen receptor. "Even when prostate cancers reach very advanced stages, they remain responsive to interventions that either suppress androgen production or block the androgen receptor," says scientist Jun Luo, Ph.D. "However, not all patients benefit from this drug." In fact, an estimated 20 percent to as many as half of men who are eligible to take this drug show no response to it.

Not every drug is effective in every man.

So how does a man know, without having to take enzalutamide for weeks or months, if he's in the group who could be helped by it? Luo and oncologist Emmanuel Antonarakis, M.D., have been working to develop a blood test that can spare men the trouble and expense of taking a drug that won't fight their cancer. The key, they believe, is a faulty androgen receptor (AR) molecule called AR-V7, which was discovered in Luo's laboratory in 2008. "It is an abnormal version of the androgen receptor," says Luo, "and it's missing the part of the AR molecule to which enzalutamide binds." In men with AR-V7, the drug acts like a key that doesn't fit the right lock – it doesn't connect. "The androgen receptor axis remains active even when the normal receptor is blocked by enzalutamide," Luo explains, and men with this aberrant molecule do not respond to the drug.

It has not been easy to translate this idea from the laboratory into the clinic. First, Antonarakis and Luo worked together to see whether AR-V7 could be detected in blood samples by examining circulating tumor cells in men with advanced prostate cancer. They found that it could. The next major hurdle has been to find out whether the presence of AR-V7 foretells the treatment response to enzalutamide. "Our hypothesis is that men who have a normal AR molecule will respond favorably to enzalutamide, while men who harbor the AR-V7 molecule will demonstrate resistance to the drug."

If their theory is proven correct, it will not only offer men a simple blood test that will help guide their treatment; this work also points to a direction for drug development – "the discovery of new drugs that also target the AR-V7 molecule," says Luo, "of which there currently are none."

How Watching Your Weight and Exercising Might Affect Your Prostate Cancer Risk

Why is it that obese men are more likely to develop aggressive prostate cancer, and to die of it? "One possible biological mechanism that underlies the association between obesity and prostate cancer is telomere shortening," says epidemiologist Corinne Joshu, Ph.D., M.P.H.. Telomeres are like aglets on shoelaces – little tips that protect the ends, except these tips are repetitive DNA sequences, and what they're protecting from wear and tear are the ends of chromosomes. "Short telomeres can cause the chromosome to become unstable, and this abnormality is strongly associated with cancer" says telomere biologist Alan Meeker, Ph.D.

Joshu, Meeker, and colleagues including Christopher Heaphy, Ph.D., and Elizabeth Platz, Sc.D., M.P.H., have been investigating telomeres as part of a larger look at how obesity influences prostate cancer development and progression, with the hope of developing new strategies for treating the disease – and ideally, for preventing it. A previous study, led by Meeker and Platz in collaboration with colleagues at Harvard University, found that men with shorter telomeres in prostate cells near their tumor, called "prostate cancer-associated stromal

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cells," had a higher risk of dying from prostate cancer.

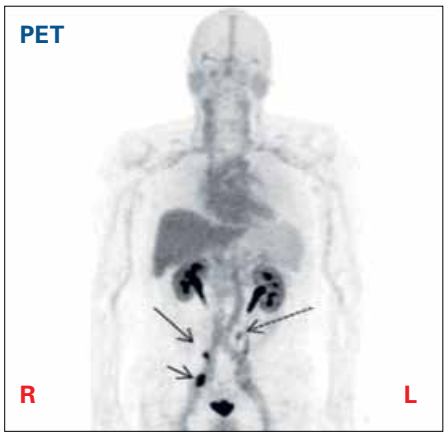
Next, the team investigated the association between obesity and telomere length in these prostate cancer-associated stromal cells. In a study of nearly 600 men who had undergone surgery to treat prostate cancer, "we found that men who were overweight or obese had telomeres that were 7.5 percent shorter in their cancer-associated stromal cells than those in men of normal weight," says Joshu. Even more striking: Men who were overweight or obese who were the least physically active had significantly shorter – by more than 20 percent – telomeres compared to men of normal weight who were the most active. "These findings not only suggest that telomere shortening in prostate cells is associated with obesity and low physical activity levels," says Joshu, "but it also may be one mechanism through which lifestyle influences prostate cancer risk and outcomes."

Your lifestyle may increase – or reduce – your risk of cancer.

"Our work on telomeres and prostate cancer will be helped tremendously by the recent acquisition of a state-of-the-art, automated fluorescence microscopy slide scanner, which was funded by the generous contribution of the donors," says Platz. This new equipment, Meeker adds, "will dramatically accelerate our telomere-based research on tissues, and will also open up new research avenues such as protein biomarker studies."

Detecting the Unseeable: Metastatic Prostate Cancer

Thanks to molecular imaging, scientists can actually see small bits of prostate cancer that have spread to other sites in the body. A recent breakthrough in molecular imaging research is a new agent, developed in the lab of Martin Pomper, M.D., Ph.D., which attaches a radioactive tag – one molecule at a time – only to prostate cells. "It targets PSMA, the prostate-specific membrane antigen, which sits on the surface of prostate cancer cells," explains Pomper, "and then this compound is visible on a PET scan." In December 2012, Pomper and colleagues published their discovery of the first small-molecule imaging agent that targets PSMA for PET imaging. That paper, published in the *Journal of Nuclear Medicine*, won the Editor's Choice Award as one of the journal's top three articles of the year.



Arrows show prostate cancer metastases.

"Molecular imaging can not only detect small amounts of disease for staging cancer, but also can be used to monitor how well treatment is working, and potentially to help us understand the biology of the disease in a particular patient," says Pomper. "We have a second-generation version of this compound that has recently completed toxicity studies, and we hope to move it fully to the clinic and test it against our original compound."

In other work, Pomper's lab has developed a system for imaging and potentially treating prostate cancer. "It makes sense that if we can target these compounds with an imaging agent, we might also be able to target them with cancer-fighting drugs or radiation. In our preclinical studies, the imaging portion of this project has proven more sensitive than the current clinical standards." Graduate student Akrita Bhatnager, who works in Pomper's lab, recently presented this work at a joint meeting of the American Association for Cancer Research and the Society of Nuclear Medicine and Molecular Imaging.

What to Do If PSA Comes Back After Surgery? New Test May Help

The numbers are troubling: About 240,000 men in the U.S. are diagnosed with prostate cancer each year. Of those, about half – 120,000 – will undergo radical prostatectomy, and of those, about a third, 40,000 men, will eventually have a return of PSA, or a "biochemical recurrence" of cancer. "These men present a management dilemma to many clinicians," says urologist Ashley Ross, M.D., Ph.D. "In fact, there are no standardized management plans for these men, and this is primarily because their experiences are so varied." Some men with a rising PSA after radical prostatectomy eventually develop metastatic cancer; in others, cancer returns at the local site and can be treated successfully with radiation. And for some men, the only sign that at least a few prostate cancer cells still exist is the fact that PSA shows up in a blood test. "Even among men who experience metastasis after a biochemical recurrence, the time to metastasis can vary over an order of magnitude."

Using a newly developed clinical test based on the specific pattern of gene expression from the primary tumor, Ross, with urologist Edward Schaeffer, M.D., Ph.D., and colleagues from GenomeDX and the Mayo Clinic found that they could help predict which men with an elevated PSA after radical prostatectomy will go on to develop metastatic disease. Although further studies are required to confirm their findings, "these results suggest that this molecular test can be used to better identify men who will need more intense, or earlier treatment at the time of their PSA recurrence, and which men will not need additional treatment and can be spared having to go through it."

"Some of these men live for many years and do not die of their cancer, while others experience early metastasis."

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Men at Very High Risk

In other news, Ross, Schaeffer, and urology resident Debasish Sundi, M.D., have defined a new subgroup of men with localized prostate cancer: men at very high risk. "When you look at what the National Comprehensive Cancer Network (NCCN) defines as high-risk prostate cancer," says Ross, "you can see that some of these men live for many years and do not die of their cancer, while others experience early metastasis even after aggressive local treatments." Ross, Schaeffer and Sundi believe this category is too broad. To help define it, and to offer more specific guidance for men with high-risk disease, they searched the Johns Hopkins radical prostatectomy database and identified more than 750 men who fit the NCCN standard of having high-risk localized prostate cancer: These men had a Gleason score between 8 and 10; a PSA greater than 20 ng/ml; or a clinical stage of T3 or higher. "We found that 15 percent of these men could be defined as being of very high risk," says Ross. Men in this subgroup had a primary Gleason pattern 5 found at biopsy (note: this is not the Gleason sum, which is obtained by adding the most common and second-most common cancer cell patterns); or five or more cores of cancer found at biopsy with a Gleason sum of 8 to 10; or multiple NCCN high-risk features (listed above). "These men had a risk that was three times greater, when compared to other high-risk men, of having metastasis and death from prostate cancer after prostatectomy. We hope that when these very high-risk men are identified, their doctors can counsel them on getting the best treatment possible," which may include surgery, radiation, and cancer-fighting drugs or hormonal therapy, and also participation in clinical trials.

Protective Gel Lowers Risk of Side Effects

An exciting breakthrough in the mechanics of delivering radiation treatment to the prostate may help prevent one of the most common side effects: bleeding from the rectum. Radiation treatment planning and delivery keeps getting better, and advances in recent years – including intensity-modulated radiation therapy (IMRT) and the use of imaging to target the radiation more precisely to the prostate – have reduced many complications, says radiation oncologist Danny Song, M.D. "But the rectum has remained at risk because of its location." The rectum and prostate are immediate next-door neighbors; think of townhouses sharing a wall. The anterior wall of the rectum is little more than a hair's breadth from the prostate, and this part of the rectum receives a high dose of radiation during treatment for prostate cancer. "About 5 to 15 percent of patients develop bleeding from the rectum several months after treatment is completed," says Song.

The rectum and prostate are immediate next-door neighbors; think of townhouses sharing a wall.

If there were just a bit more distance between the rectum and the prostate, much of this damage could be avoided. In an effort to create that space, Song and Theodore DeWeese, M.D., Ph.D., Chairman of Radiation Oncology and Molecular Radiation Science, have been working with a temporary filler – a biodegradable gel. "Polyethylene glycol is a substance that has been around for years and is used in several medications," says Song. "When it is turned into a gel, it doesn't last forever; it is eventually broken down and absorbed by the body."

But what this gel does is provide a much-needed cushion. In previous experiments using cadavers, Song and DeWeese successfully showed that they could inject polyethylene glycol between the rectum and prostate and push the rectum away from the danger zone, the high-dose radiation target area. With clinical collaborators in Europe, Song and DeWeese recently demonstrated that men who were injected with the gel before they started radiation treatment had "significant reductions in the amount of radiation received by the rectum," says Song, "and these patients went on to have very low rates of rectal toxicity." Based on this work,

What this gel does is provide a much-needed cushion. It pushes the rectum away from the danger zone, so that the radiation only goes to the tissue that needs it: the prostate.

FDA approval for the gel is pending. "Soon, our patients who are starting radiation treatment for prostate cancer will be offered the ability to receive this side effect-sparing treatment." This work is currently in press with the *International Journal of Radiation Oncology, Biology, and Physics*.

Building a National Radiation Oncology Registry

How good are external-beam radiation and brachytherapy at killing prostate cancer? Do results vary depending on the institution? Is one form of radiation, or a particular dose, more effective than another? What about the addition of temporary hormonal therapy to radiation therapy in men at high risk of recurrence? Radiation oncologist Phuoc Tran, M.D., Ph.D., believes the best way to find out is with a National Radiation Oncology Registry. With colleagues from top-ranked institutions nationwide, he has established a pilot registry that he hopes will get this project started. This effort was recently chronicled in the *Journal of Oncology Practice*.

"The pilot registry, which uses a consensus-based set of prostate cancer data elements as a model, will provide the framework for expanding to a national electronic registry for radiation oncology in the United States," he says. The National Radiation Oncology Registry is a national collaborative initiative between the Radiation Oncology Institute and the American Society for Radiation Oncology. Its mission, says Tran, "is to improve the care of cancer patients by capturing reliable information on treatment

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delivery and health outcomes." Prostate cancer has been selected for this pilot, he adds, because of its "high incidence, multiple management options, potential public health and economic implications, and because it was identified by the Institute of Medicine as the area of oncology most in need of comparative effectiveness research."

A national registry "would yield invaluable quality improvement potential by focusing on best practices, treatment effectiveness, and practice patterns of care," Tran adds. "Benchmarking across institutions will promote rapid learning and accountable cancer care, and will benefit patients through improved health outcomes." With such a registry, doctors can evaluate how well men do with specific doses and treatments, "and this will transform our efforts to improve quality and safety in radiation oncology."

Teaching Computers to Tell Cancer Cells Apart

Prostate cancer is notoriously difficult for pathologists to reproducibly read and interpret. It is a jumble of cell types in the tissue – normal cells mixed in with not just cancer cells, but several different kinds of cancer cells. Prostate cancer cells have different Gleason pattern numbers assigned based on their morphology – how their size, shape and orientation appear under the microscope. Scientist Robert Veltri, Ph.D., working with a biomedical engineer from Case Western Reserve University, Anant Madabhushi, Ph.D., has come up with a way for a computer to help. Veltri has been studying the structure of the nucleus of prostate cancer cells for years, and that expertise is now part of an automated tissue-studying program that uses seven key structural features to analyze Gleason grade. "The computer program needs only three out of seven features to distinguish with 90 percent accuracy Gleason grade patterns 3 and 4, and to differentiate aggressive from non-aggressive prostate cancer," he says.

Blood Transfusion and Radical Prostatectomy

It doesn't happen nearly as often as it used to, but some men who undergo radical prostatectomy need to have extra blood – either from a donor, or from a supply of their own blood, banked ahead of time. "Fortunately," says urologist Misop Han, M.D., "the need for blood transfusion with radical prostatectomy has been gradually decreasing with the discovery of important anatomic structures around the prostate gland by Patrick Walsh, and the increasing use of minimally invasive surgical techniques."

For men who may need it, there is good news: Getting a blood transfusion does not affect your chances for cure.

But for the men who may need it, there is good news: It does not affect a man's chances for cure. In a study led by Han, investigators looked at the large database of men who underwent radical prostatectomy at Johns Hopkins between 1994 and 2012. "We found that blood transfusion, whether from a donor or using your own blood, does not independently affect your risk of recurrence or your length of survival after surgery. Also, the amount of blood transfused did not change the outcome," Han reports. These results were presented at the annual meeting of the American Urological Association in San Diego.

Coffey Honored

Donald Coffey, Ph.D., the *Catherine Iola and J. Smith Michael Distinguished Professor of Urology*, was named one of the 100 initial Fellows elected by the The American Association for Cancer Research to its newly formed and prestigious Academy. The Academy recognizes and honors distinguished scientists whose major contributions have propelled significant innovation and progress against cancer. The Fellows were selected through a rigorous review process. Coffey was elected along with two other Hopkins scientists: Bert Vogelstein, M.D., and Nobel Laureate Carol Greider, Ph.D.

WANT TO LEARN MORE? To find earlier issues of *Discovery* and *Prostate Cancer Update* — and much more — check out our website: http://urology.jhu.edu

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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 promising scientists at Johns Hopkins in every discipline: "If," we tell them, "you have a good idea worth pursuing that can help us further our understanding of prostate cancer and help us find the cure, apply for funding." Then, if our Scientific Advisory Board thinks it's worth pursuing, we provide $75,000 a year for two years to support pilot projects to test these ideas. This provides the investigator with valuable preliminary data to use when applying for continued support from agencies like the National Institutes of Health. This unique Fund is only possible because of great generosity, from you, our wonderful patients and friends who share our commitment to curing prostate cancer. Our scientific advisory board is made up of distinguished Hopkins scientists and two lay members, Christian Evensen and Samuel Himmelrich. Some of the exciting work of the investigators funded this year is described below.

2013 Awardees

Stephen Gould, Ph.D.

Hans-Joerg Hammers, M.D., Ph.D.,
The Peter Jay Sharp Foundation Scholar

Daniel Leahy, Ph.D.,
The Phyllis and Brian L. Harvey Scholar

Barry Nelkin, Ph.D.

Karen Sfanos, Ph.D.,
The Beth W. and A. Ross Myers Scholar

Phuoc Tran, M.D., Ph.D.,
The Irene and Bernard L. Schwartz Scholar

Srinivasan Yegnasubramanian, M.D., Ph.D.,
The R. Christian B. Evensen Scholar

2013 Awardees, receiving 2nd year of funding

Michael Caterina, M.D., Ph.D.

Samuel Denmeade, M.D.,
The Carolyn and Bill Stutt Scholar

William B. Isaacs, Ph.D.,
The Dr. and Mrs. Peter S. Bing Scholar

Marikki Laiho, M.D., Ph.D.

Shawn Lupold, Ph.D.,
The Nancy and Jim O'Neal Scholar

Dan Stoianovici, Ph.D.,
The Virginia and Warren Schwerin Scholar

Exosomes and Prostate Cancer

Just as a dandelion sends forth its seeds, cells in our bodies release tiny, self-contained pods called extracellular vesicles (EVs). But unlike dandelion wisps that scatter in the wind, these EVs are sent in specific directions, as if the cell says, "Go out the back door," or "Go to the street." Once they're launched, EVs get busy. Each one carries an abbreviated, condensed version of the cell's proteins and genetic information and as an EV moves from one cell to another, it causes little changes in the cells it touches. "EV production is amplified in prostate cancer," says geneticist Stephen Gould, Ph.D., professor of biological chemistry, "sometimes as much as 10 times higher than in normal cells." The problem is that the contact between a cancer-made EV and a normal cell can be harmful. These EVs "have been shown to promote cancer growth and metastasis by delivering signals and molecules to neighboring cells." Basically, as the EVs transfer genetic material from the "mother ship" – the cancer cell that made them – they reprogram neighboring cells to create a friendlier environment where cancer is more likely to thrive. "For example, cancer-derived vesicles can cause endothelial cells to make new blood vessels to feed the tumor," notes Gould, "and can silence cells of the immune system that might otherwise attack and kill the tumor cells."

As the EVs transfer genetic material from the "mother ship" – the cancer cell that made them – they reprogram nearby cells to create a friendlier environment where cancer can thrive.

With co-investigator William Isaacs, Ph.D., the *William Thomas Gerrard, Mario Anthony Duhon and Jennifer and John Chalsty Professor of Urology*, Gould is using his award from the Patrick C. Walsh Prostate Cancer Research Fund to characterize EVs made by prostate cancer cells. The scientists are identifying the specific proteins and RNA material released by the cells, and testing to see if they can affect the production of these vesicles. They also hope to find out the role EVs play in cell-to-cell communication; particularly, how they transmit RNA and other genetic material from prostate cancer cells to normal cells. Gould believes this work will produce several potential targets for new ways to treat prostate cancer.

Keeping Cancer from Growing by Sabotaging Its Infrastructure

Hans-Joerg Hammers

Imagine trying raise a barn without getting the framework ready first: It would be a disaster. Without infrastructure, you couldn't build much of a barn – or a road, or anything else, for that matter. The same holds true for prostate cancer. Without an infrastructure in place, a cancer can't do much growing. Prostate cancer that can't spread: wouldn't that be wonderful?

Oncologist Hans-Joerg Hammers, M.D., Ph.D., the *Peter Jay Sharp Foundation Scholar*, is hoping that by blocking a new target – a particular fragment of collagen that is critical in helping cancer grow – he can achieve success that has so far eluded other scientists

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THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND

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seeking to stop prostate cancer from spreading to distant sites.

"Prostate cancer cells don't grow in isolation," he explains. "In fact, for them to expand in size and to spread to the bones, they have to coax normal cells into helping them." Cancer cells, it seems, are good at drumming up recruits – getting their neighbors to help raise the barn. "Prostate cancers make surrounding cells produce new matrices and scaffold protein." This structural support not only helps the cancer cells grow, but "appears to be critical to the formation of new blood vessels to feed them." These neighborly volunteers – normal cells called fibroblasts – together with their newly formed matrix are known as stroma.

"The activation of stroma is intimately linked to prostate cancer," says Hammers, "particularly with more aggressive disease. It is also a hallmark for the abnormal bone changes that happen in men with metastatic prostate cancer." Previously, scientists hoped to stop cancer from paving the road ahead with new blood vessels – a process called angiogenesis – by targeting a pathway that involves these blood vessels. Unfortunately, this pathway, called "vascular endothelial growth factor, or VEGF," has not panned out as a way to stop metastasis.

"The VEGF pathway has failed now in several large Phase III clinical trials," notes Hammers. He believes that the stroma may make a more vulnerable and accessible target. Exciting findings by Hammers' laboratory have shown that before new cancer blood vessels can be made, other things have to be made first: The cancer cell must construct new matrix, or scaffolding; also, a certain bit of collagen has proven to be critical for the formation of blood vessels to supply new growth.

With funding from the Patrick C. Walsh Prostate Cancer Research Fund, Hammers is working to develop new agents that will block this part of the construction. Although the target is small, if it proves as important as Hammers hopes, the result might be for the cancer cell like a carpenter trying to connect boards without nails – a nonstarter.

Blocking a Protein that Allows Prostate Cancer to Grow

Scientists believe that cancer results from a bunch of tiny hits to the body – damage to the genes that can simultaneously result in accelerated growth, which happens in cancer, and a shutdown of other cells that normally could suppress cancer. Tumor suppressors are genes whose job is to keep cells from turning down a bad road that could lead to cancer. Normally, these genes check cells for signs of abnormal growth and then put a stop to it. But many cancer cells know how to get around this defense: They simply turn off the supply of tumor suppressors. They do this by a process called DNA methylation – basically, structural changes to DNA that keep it from functioning the way it's supposed to.

This protein does what soldiers are taught to do: It secures the perimeter.

Daniel Leahy, Ph.D., *The Phyllis and Brian L. Harvey Scholar*, is investigating a particular protein involved in methylation. This protein, called MBD2 (for "methyl-CpG Binding Domain Protein"), does what soldiers are taught to do: It secures the perimeter. MBD2 binds to methylated regions of DNA and squelches the ability of nearby genes to fight off cancer. "In mice and in cancer cells studied separately, when MBD2 function is lost, this slows down rampant cell growth," says Leahy, professor of biophysics and biophysical chemistry. "We think this is because it allows the tumor suppressors to come back."

Surprisingly, he adds, "blocking MBD2 in mice does not cause any notable side effects." Could an MBD2-blocking drug help the body fight off prostate cancer? With co-investigator William G. Nelson, M.D., Ph.D., the *Marion I. Knott Director* of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Leahy is hoping to find out. The Nelson lab has developed a way to screening for MBD2 activity, and "we are beginning to screen more than 300,000 compounds to see whether they inhibit MBD2," at a facility in Florida. The ultra-exact screening process includes using X-ray crystallography to look at the atomic structure of MBD2 as it is bound to methylated DNA. "We have grown crystals of the methyl binding region of MBD2 bound to methylated DNA," says Leahy. "Having this structure will reveal the precise chemical contacts that MBD2 uses to recognize DNA. Knowing the chemical nature and shape of these regions will guide efforts to design and improve inhibitors of MBD2. We also hope to gain insight into how MBD2 recognizes methylated DNA," which also should prove very helpful as scientists develop drugs aimed at this new and promising target.

Although Leahy believes the screening process will identify many– maybe even hundreds – of potential MBD2 inhibitors, "these molecules are unlikely to possess optimal drug attributes," and likely will need some pharmacologic tinkering to help produce the most effective drug against prostate cancer.

A Dramatic Boost in the Body's Ability to Suppress Prostate Cancer

Barry Nelkin

The body's immune system fends off more threats than we may ever realize. It is remarkably successful in keeping us healthy. But in diseases such as prostate cancer, the immune system is sabotaged in insidious ways. One culprit is a protein called CDK5. In mouse studies, Barry Nelkin, Ph.D., professor of oncology, has discovered that deleting the CDK5 gene in prostate cells provides a hefty boost to the body's immune system and dramatically lengthens survival.

Nelkin believes this research has the potential to help prolong life in men with metastatic prostate cancer. Advanced cancer cells are difficult to kill for many reasons; one is that cancer-fighting drugs target tumors in very specific ways, and don't always have the same effect in every man. "There is an urgent need for better therapies

for advanced prostate cancer that can be applied to the majority of patients," says Nelkin. "Immunotherapy, because it targets the body's immune response rather than a specific feature of the tumor itself, has the potential to fill this need."

Think of a situation in nature where an invasive plant or insect has no natural predators, and disaster results. In cancer, the natural balance is thrown off in two major ways: An invasive set of cells is introduced, and the body's ability to kill it is compromised. Scientists have long been excited about the potential of immunotherapy to boost the body's own defenses so that it can fight off cancer, but despite tremendous advances in this field, there has been no "home run" immunotherapeutic drug that has managed to succeed against prostate cancer. "Improvements in the efficacy of immune modulation for anti-tumor response are critically needed," says Nelkin. He believes that new approaches, including combining forms of therapy, may have better success. "Our preliminary data shows the exciting prospect of such a new approach to immunotherapy – modulating the immune response by targeting signaling pathways within the tumor cells."

With support from the Patrick C. Walsh Prostate Cancer Research Fund, Nelkin is pursuing his lab's exciting early findings that suggest targeting CDK5 may be the way to go. In mouse models, "we have found that prostate-specific deletion of the CDK5 gene resulted in a dramatic survival benefit." After treatment, the prostate tumors in these mice "unexpectedly showed significant differences in expression of a variety of genes related to inflammation and immune response," including immune system-stimulating proteins that regulate T cell function. T cells are elite immune system warriors, powerful lymphocytes, or white blood cells, that protect against infection. "When we deleted the CDK5 gene, there was a dramatic activation of T lymphocytes compared to mice in the control group," says Nelkin. "These findings suggest that the impressive tumor-suppressive effects of getting rid of the CDK5 gene in the prostate may be happening, at least in part, because the antitumor immune response has been turned up."

Nelkin is now working to understand the specifics of how this works in detailed further studies. If this form of immunotherapy is as successful as Nelkin envisions, it could lead to a new form of therapy for prostate cancer, "in which CDK5 would be inhibited pharmacologically, likely followed by further specific modulation of the anti-tumor immune response. If our hypothesis is correct, rapid translation to applying this in men with prostate cancer is possible, since drugs that inhibit CDK5 are already in clinical trials."

"Acne Bacteria," Chronic Inflammation, and Prostate Cancer

WA few years ago, when Karen Sfanos, Ph.D., the *Beth W. and A. Ross Myers Scholar*, was a graduate student in the laboratory of William Isaacs, Ph.D., the *William Thomas Gerrard, Mario Anthony Duhon and Jennifer and John Chalsty Professor of Urology*, she went to a meeting. Patrick Walsh, M.D., was also there, and the discussion centered around a recent report in the medical literature that a certain species of bacteria, *P. acnes* – the same kind of bacteria that plagues teenagers worldwide by causing acne – was found in prostate cancer specimens, and was more likely to be found in prostate tissue that also contained inflammation. Could a bacterial infection lead to prostate cancer? There is reason to believe that it might. A number of Hopkins scientists including Isaacs, Angelo De Marzo, M.D., Ph.D., William Nelson, M.D., Ph.D., and Elizabeth Platz, Sc.D., have been studying the possible link between bacterial infections and prostate cancer, alerted by pathologists who found unexplained inflammation and inflammation-associated tissue damage in biopsy samples and in prostate specimens examined after radical prostatectomy. Brady scientists have been at the forefront of those making these discoveries and asking further questions.

"As many as 20 percent of all human cancers are associated with infections, either as a direct cause or as a contributing factor," says Sfanos. In other words, maybe the infection itself does not cause cancer, but it leads long-term inflammation, and this creates a more hospitable environment that ultimately allows cancer to develop. With so many cases of cancer linked to infection, "this represents a significant global cancer burden, as well as a tremendous opportunity for cancer treatment and prevention strategies with antibiotics and vaccines."

But this particular form of bacteria? "It is ubiquitously present on human skin," and this has posed a problem for scientists trying to investigate it. Was it truly an infection within the prostate, or was there just some unintentional contamination of the bacterial culture from the skin or surgical environment? After that meeting, Sfanos studied prostate tissues from men undergoing treatment for prostate cancer and confirmed that *P. acnes* can indeed be cultured from prostate tissues; her findings were published in 2008 in *The Prostate*. With further encouragement from Isaacs and Walsh, Sfanos, now an assistant professor of pathology, has continued to study the potential of role of *P. acnes* as a cause of long-term inflammation that leads to prostate cancer.

In one recent study, Sfanos's group used a new technique called MultiLocus Sequence Typing to categorize the types of *P. acnes* that they found in prostate tissue samples. "We found that the strains of *P. acnes* isolated from the human prostate are related to strains of *P. acnes* found in the male urinary tract, or found in opportunistic infections – as opposed to strains that are associated with severe acne." The results of this study, published in *The Prostate*, suggest that these prostate-growing strains do not simply represent contamination from the skin.

Maybe the infection itself does not cause cancer, but leads to long-term inflammation, and this ultimately allows cancer to develop.

But exactly what these bacteria are doing in the prostate has been challenging to determine. To find out more, Sfanos and colleagues have turned to mice – specifically, to a mouse model of inflammation in the prostate developed using one of the *P. acnes* strains Sfanos isolated from human prostate tissue samples. "In our studies of prostate infections in mice, we have observed that a

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single bacterial infection can cause chronic prostate inflammation that persists for months after the initial infection," she says. Based on these and other findings, Sfanos believes that there may be a long lag time – years, or even decades – between an initial bacterial infection, the development of chronic inflammation, and the development of prostate cancer. These findings also were published in *The Prostate*.

With support from the Patrick C. Walsh Prostate Cancer Research Fund, Sfanos is now studying the long-term effects of different bacterial strains in infected mouse prostates, and evaluating the inflammation that these bacterial strains cause. "We aim to study the potential pathogenic effects of long-term infection and chronic inflammation for six months to a year, produced by different species of bacteria in infection models of the mouse prostate." Sfanos and colleagues are looking at blood and prostate tissue for inflammatory cytokines, cells made by the immune system, in hopes of learning more about how the body reacts to specific bacteria. "The ultimate translation of our studies would be to compare the inflammatory responses that we observe in mice to the inflammatory responses observed in the human prostate, and in human prostate cancer."

A Drug to Make Radiation More Effective in High-Risk Men

How can we improve the likelihood of a cure for men with high-risk and locally advanced prostate cancer? Radiation oncologist Phuoc T. Tran, M.D., Ph.D., the *Irene and Bernard L. Schwartz Scholar*, believes the answer lies in making prostate cancer cells more vulnerable to radiation. "More than 30 to 40 percent of men with high-risk and locally advanced prostate cancer who are treated with definitive radiation therapy experience biochemical failure." In response to this, scientists have made radiation therapy more effective in high-risk men by increasing the dose – which has helped, to a certain extent. But the radiation dose can only be bumped up so high before it causes side effects, damaging nearby rectal and urinary tract tissue.

Special, tumor-specific agents may make the cancer more sensitive to radiation – so that each dose of radiation packs more of a punch.

So, how to protect normal tissue but make the radiation more effective? Special, tumor-specific agents called radiosensitizers may be able to make the cancer more sensitive to the radiation – so that each dose of radiation packs more of a punch. One such class of agents targets HSP90. "HSP90 is a molecule that's present in abnormally high amounts in prostate cancer cells," Tran notes. "It helps stabilize proteins that are necessary to keep prostate cancer cells alive, and also makes them resistant to radiation."

In early tests, HSP90-targeting drugs worked well in the laboratory and in phase I and II clinical trials, but were not very well tolerated by patients. A next-generation drug, ganetespib, looks much more promising. "In the laboratory, ganetespib exhibits potent activity in a broad range of human cancer cells, including prostate cancer," says Tran. "In addition, we showed that next-generation HSP90 inhibitors are potent radiosensitizers of prostate cancer cells. Moreover, ganetespib displayed superior pharmacological and safety properties compared to the earlier drugs and is currently undergoing clinical evaluation in multiple cancer Phase I and II trials," although it is not being tested against prostate cancer.

Because ganetespib is performing so well, Tran believes it will be a potent, tumor-specific radiosensitizer for prostate cancer. With support from the Patrick C. Walsh Prostate Cancer Research Fund, he will begin a Phase I clinical trial of ganetespib along with temporary hormonal therapy in men with high-risk or locally advanced prostate cancer. Currently, hormonal therapy is given to these men for a long period because it makes radiation therapy more successful. Tran believes adding the radiosensitizer will prove an effective triple-threat. "We expect to find the appropriate dose of ganetespib to be used in combination with radiation and hormonal therapy, and lay the groundwork for future Phase II and III trials," he says. "It is exciting that we will be targeting critical pathways that prostate cancer needs to survive and become resistant to radiation."

A Closer Look at Chronic Inflammation and Prostate Cancer

There is a fine line between perfection and overkill. Take the body's immune system, for instance: "It can be quite powerful in mounting a defense against foreign organisms like viruses and bacteria," says oncologist Srinivasan Yegnasubramanian, M.D., Ph.D., *The R. Christian B. Evensen Scholar*. "However, it is now well recognized that the immune system can also damage our own tissues, causing a sort of collateral damage while it wards off threats to the body." This collateral damage can even last for years, he adds. Under the microscope, this damage often shows up as chronic inflammation near the damaged tissue.

Increasingly, scientists are finding this type of chronic inflammation in the prostate – particularly, in the prostates of men who eat the "Western" diet, heavy in fat and light on fruits and vegetables. Scientists at Hopkins and elsewhere have found a strong link between this inflammation and the development and progression of prostate cancer. "This inflammation has been linked to many factors, including infections in the prostate, the diet, hormonal factors, and tissue damage from trauma and urine reflux," says Yegnasubramanian. "However, despite this mounting evidence, it is still unclear whether this inflammation in the prostate is actually causing prostate cancer or not. And, if it is causing prostate cancer, what is happening on the molecular level?"

Yegnasubramanian is working to find out, with support from the Patrick C. Walsh Prostate Cancer Research Fund. "One reason that we don't understand the underlying molecular basis has been that we don't have good models that can examine the complex interplay between the immune system and prostate function and disease," he notes. But now, Yegnasubramanian and colleagues Angelo De Marzo, M.D., Ph.D., and University of Maryland Baltimore County

scientist Charles Bieberich, Ph.D., have developed and started to characterize a cutting-edge, genetically engineered, new model system in mice that can closely mimic the particular inflammation seen in the human prostate. "In this model system, we can turn the propensity for chronic inflammation on and off, and examine the effects of prolonged, acute, and episodic inflammatory stress on the prostate."

With this new model system, Yegnasubramanian and his collaborators De Marzo and Bieberich hope to learn whether chronic inflammation can "directly lead to formation of prostate cancer after prolonged or recurrent stress." The scientists also will examine whether this is more likely in mice that – just like some men – have a predisposition to developing early stages of prostate cancer. And what about after cancer develops? Does chronic inflammation make it advance more quickly? Does it make cancer more likely to metastasize? Yegnasubramanian suspects that it might, by causing minuscule changes at the most fundamental level. "Based on compelling data from our lab, we hypothesize that inflammation may cause cancer formation and progression through molecular damage to the machinery that helps to interpret genetic instructions – the so-called epigenetic machinery."

This type of chronic inflammation is increasingly common in the prostates of men who eat the "Western" diet, heavy in fat and light on fruits and vegetables.

In groundbreaking research, by harnessing the latest innovations in whole-genome analysis, Yegnasubramanian and colleagues will be able to study the alterations in the epigenome that are caused by inflammation. "These studies will allow us to develop a better understanding of how inflammation can lead to the formation and progression of prostate cancer." They also, he hopes, "will ultimately allow us to develop rational approaches for treating and even preventing prostate cancer."

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"It's gone. The cancer is gone."

Susan and Bob Bruce

"I don't even remember exactly when I had it," says Bob Bruce, and believe it or not, this is the best possible news for us here at the Brady Urological Institute. "This is what we hope will happen," says surgeon Alan W. Partin, M.D., Ph.D., Director of the Brady. "Ideally, prostate cancer will be a very finite incident in a man's life, something that we diagnose, we treat, we cure, and then the man moves on and lives the rest of his life."

This is what has happened to Bob. It was early spring six years ago: Bob was 60 and his PSA was slightly elevated. It was still very low, but it had gone up from 1.9 to 2.2, and his local urologist in Virginia recommended that he get a biopsy. "It came back that some of the samples were cancerous," Bob says. The urologist advised him to have surgery. "I said, 'Let me get another opinion,'" and Bob came to Hopkins. He met with Partin – still not certain whether he would have surgery and, if he did have it, where he should have it done. "After I talked to him, it was very apparent to me that I was going to have my prostate taken out, and for my peace of mind, I was going to have it done at Johns Hopkins."

Bob scheduled the operation for August, after he and his wife, Susan, took a vacation. The day after the procedure, Partin told Bob that everything looked great, and that he could go home. The pathology results came back with good news: "It's gone. The cancer is gone. I haven't looked back since." When he started talking about his experience, Bob was surprised to find out how many of his friends had gone through their own bout with this disease. "Nobody ever talks about it," he says, until someone joins the "reluctant brotherhood" – the ranks of men with prostate cancer. One of his friends was diagnosed when

"After I talked to him, it was very apparent to me that I was going to have my prostate taken out, and for my peace of mind, I was going to have it done at Johns Hopkins."

cancer had already escaped the prostate, and the cancer proved fatal.

Bob is thankful for his early diagnosis. "There's a controversy over PSA testing, but I credit me still being here to PSA testing." Bob, now 66, has been a generous supporter of work at the Brady Urological Institute to improve diagnosis and treatment of prostate cancer, and to further understanding of the genetic factors that can cause the disease to run in families. Bob has two sons, ages 30 and 34, and knows that "they're certainly at risk – because they're my sons," he says. Bob has recommended the Brady to his friends, and one reason is that the Brady treats so many men with prostate cancer that "if you're unlucky and something goes wrong, chances are that they've seen it before, and dealt with it before. I just had a positive experience all the way around."

Bob's many gifts over the years since his surgery "have made it possible for us to evaluate and assist on Food and Drug Administration approval of three new tests for the early detection of prostate cancer," says Partin, who has been at the forefront of investigating and developing new biomarkers that can be more cancer-specific and do a better job of prediction than the PSA test. "The Brady Urological Institute was begun nearly a hundred years ago with the philanthropy of 'Diamond Jim' Brady," Partin adds. "He was a kind and generous man who felt very fortunate that he had come to Johns Hopkins. He had many complicated health problems, and no other institution in the world had been able to cure his benign prostatic enlargement. So he decided to return the favor. When people like James Brady and Bob Bruce give back, they are enabling us to do more than we otherwise could to find new treatments for our patients."