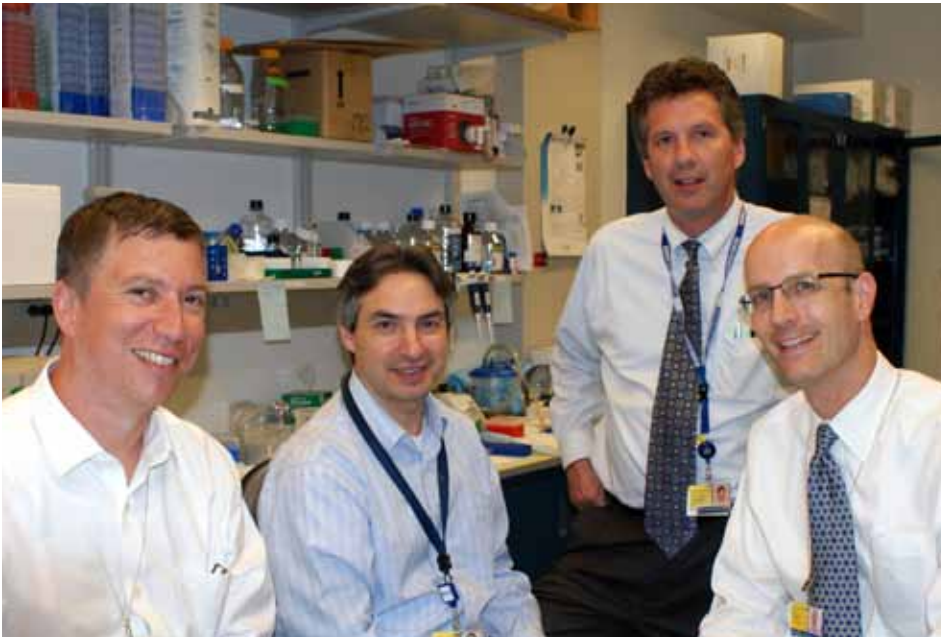


# DISCOVERY

The Brady Urological Institute • Johns Hopkins Medicine

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



*The Fund, designed to “think outside the box” in a smart, creative way, has supported the work of Hopkins’ finest scientists, including (from left), David Berman, Angelo De Marzo, Bill Nelson, and Edward Schaeffer.*

## The PCW Fund Begins Sixth Year:

*After 43 Pilot Projects,  
We’re 28 Fully Funded  
Grants and 44 Publications  
Closer to Finding the Cure*

Their ideas are promising, new, creative — yet unlikely to be funded. Too risky; in today’s research climate, money is just too tight to bet on the unknown. Grant committees often find themselves in the position, not unlike Hollywood moguls, of putting their money in “sequels” — renewing funding for established investigators, safe risks, sound investments. And this means, increasingly, that young scientists find themselves in the Catch-22 position of needing money to support their research, but not being able to get it because they don’t have a proven track record — and not being able to get a grant so they can build a track record in the first place.

At Johns Hopkins, five years ago, the Patrick C. Walsh Prostate Cancer Research Fund took a different approach. Beginning with a generous endowment, established by Walsh’s patients, their families and friends, the Fund threw open the doors for investigators throughout all of Johns Hopkins University, in any discipline. “What mattered most was that we were looking for good ideas, from the best and brightest investigators at Hopkins,” says Walsh, “who are among the finest scientific minds anywhere. And we found innovative ideas — a lot of them, and more are being submitted every year. The best of these deserve to be explored. They may work, or they may not, but if they can help us find a cure for prostate cancer, then isn’t it wonderful that we have the opportunity to give them a chance?”

The Fund, designed to “think outside the box” in a smart, creative way, is entering its sixth year of supporting new ideas.

*[continued on page 2]*

THE PATRICK C. WALSH  
PROSTATE CANCER RESEARCH FUND

### FOUNDERS’ CIRCLE

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Mr. and Mrs. Charles B. Thornton Jr.  
Luciana and Joe Vittoria

## Interesting Contradictions



*Partin: Our approach is multi-faceted.*

**As this issue was being written, the Brady Urological Institute was named the best urological center in the country by *U.S. News and World Report Magazine*, for the 20th year in a row. And yet, if you were to walk with me today through our labs and**

**clinics, you wouldn’t see any sign of our hard-working faculty, fellows, students, nurses, and staff resting on their laurels.**

**An interesting contradiction. Reading over this latest issue of *Discovery*, I came across several more. We are working to make our surgery**

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[continued from page 1]

**better than ever, with strategies to help protect the fragile nerves involved in erection, and with a robotic probe to refine the laparoscopic prostatectomy procedure. And yet, we are also conducting many multidisciplinary studies to determine which men can put off or avoid having treatment for their prostate cancer. Our active surveillance program is designed to spare men the effects of treatment — while watching them vigilantly, with the toughest standards in the country, so that at the most subtle hint that cancer is progressing, we can give them curative treatment.**

**While we are looking for better markers to detect cancer, and to predict whether it is likely to need treatment, we are working with innovative therapies to catch it at the other end, if it comes back after treatment. And, as they work on ultra-sophisticated uses of viruses and other weapons, our scientists have discovered two very low-tech strategies that can help lower a man's risk of recurrence after treatment, as well — losing weight and stopping smoking. We are studying the human genome to find ways to prevent cancer, and also working to create a better animal model, so that we can study the most aggressive forms of this disease, and bring new treatments to our patients faster.**

**We are fighting prostate cancer, even as we are proving that it is not just one disease, that it has many manifestations, and that myriad factors, including a man's race, can play a role in determining its course.**

**Basically, we are working hard to be as multi-faceted, as direct, as complex, and as simple as prostate cancer. I'm proud of the advances featured in this issue, proud of all the people here at the Brady, proud of our patients, who are working to beat this disease, and to prevent it in their sons and grandchildren, and so appreciative of everyone who has supported the Patrick C. Walsh Prostate Cancer Research Fund, for helping to make these discoveries possible.**

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

[continued from page 1]

In its five years, it has awarded \$1 million a year in prostate cancer research funds — 43 grants, to researchers in seven departments: Urology, Epidemiology, Radiology-Magnetic Resonance Research and Neuroradiology, Mechanical Engineering, Comparative Medicine, Pathology, and Oncology. The work of these scientists has resulted in 44 publications, and spawned 28 fully funded grants from the National Institutes of Health, the National Cancer Institute, the Department of Defense, the National Institute of Biomedical Imaging and Bioengineering, the Howard Hughes Medical Institute, and other agencies. (Note: All of this research has been covered in *Discovery*. This year's winning research ideas are featured on Page 15; for more on past winners, please go to the Brady's website, at: <http://urology.jhu.edu>, and click on "Newsletter" at the top of the page.)

"This has been a win-win for everybody," says Walsh, "and most of all, for our patients, who know that the brightest minds in the country are pursuing many promising leads, working to cure their cancer, and to prevent their sons from getting it." None of this, he adds, would have been possible without the remarkable private support from patients, family and friends. "I am so grateful to all of you who have contributed so generously to this cause, and I want you all to know that your precious contributions have been well invested."

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## Can Weight Gain, Smoking Make Cancer More Likely to Come Back?

So you're a candidate for a radical prostatectomy, or maybe you've just had one. There is an excellent chance that your cancer will be cured. But what if there were some pill, some dietary supplement, something extra that could help you lower your odds of recurrence even more. Would you take it? Most men would, gladly.

Well, it's not a pill, but intriguing work led by Hopkins scientists suggests that there is something that may help tip the scale — literally — away from cancer recurrence, and it has to do with gaining weight and smoking. A recent study found that men who gained five or more pounds near the time of their radical prostatectomy were twice as likely to have their cancer come back as men who maintained their weight. Men who were still smoking a year after their surgery were also more than twice as likely, compared to men who had never smoked or who had kicked the habit, to have their cancer return.

In this retrospective study, investigators

**"Taken together, these findings suggest that by maintaining a healthy weight and by not smoking, men with prostate cancer may not only help themselves stay cancer-free, but they can improve their overall health and well-being."**

surveyed more than 1,300 men who had undergone radical prostatectomy at Johns Hopkins to treat early-stage prostate cancer. Most of these men were cured of their cancer, but in 106 men, cancer returned. Could it be, the scientists wondered, that lifestyle factors might play a role here? Were the men whose cancer returned doing anything differently? The men in the study were asked to fill out questionnaires, reporting on factors like their weight, diet, and smoking, and were followed for about seven years after surgery. They were also asked to recall how much they had weighed from five years before surgery to a year afterward.

"We found that men whose weight increased by more than about five pounds during this time period had an almost two-fold higher risk of prostate cancer recurrence, as compared with men whose weight remained the same," says Corinne Joshu, Ph.D., M.P.H., a postdoctoral fellow who, with epidemiologist Elizabeth Platz, Sc.D.,



*Platz and Josbu: Looking for lifestyle changes that can help keep cancer away.*

M.P.H., carried out the study, in collaboration with urologists Patrick Walsh, Misop Han, and colleagues at the National Cancer Institute and Duke University. “This was true even among physically active men.” Although exercise certainly helps people lose weight, the key in this study seemed to be the weight change itself; the risk went up as the weight increased, and decreased with weight loss. On average, the men who had gained weight during this period reported that they’d gained about 10 pounds.

When the researchers looked for links between smoking and recurrence, they found that not only did smoking increase the risk of cancer returning, but that current smokers had a 25-percent higher risk of recurrence for every 10 pack-years smoked. (A pack-year is the number of packs of cigarettes a man smokes per day, times the num-

ber of years he has smoked.) “We found that men who keep smoking after being diagnosed with prostate cancer are more likely to have a recurrence — but that men who quit are not,” says Platz. “Taken together, these findings suggest that by maintaining a healthy weight and by not smoking, men with prostate cancer may not only help themselves stay cancer-free, but they can improve their overall health and well-being.”

This is not a definitive study, and more work is needed to confirm these findings, the researchers caution. For one thing, a larger number of men should be studied; for another, there are inherent difficulties in asking men to remember how much they weighed or how many cigarettes they smoked in the past. But it does raise questions to be pursued in other studies — including, from a basic science point of view,

what biochemical pathways are activated or maintained by smoking, and how do these affect prostate cancer? What happens to these pathways when a man cuts calories, or packs on a few pounds? Another complicating factor is that, for reasons no one understands, PSA levels tend to be lower in heavyset men, so it may take longer for follow-up PSA tests to detect a change.

“The important thing here is that being overweight and smoking cigarettes are major health problems in our country,” says Platz. “More than two-thirds of Americans weigh more than they should, and 20 percent of adult men smoke. Right now, we can’t say for certain that these factors influence the recurrence of prostate cancer. But because they are so widespread, because they lead to premature death — and because they can be prevented — it makes sense for men who have had prostate cancer not to gain weight, and to stop smoking.”

These results were presented in April at the annual meeting of the American Association for Cancer Research, held in Washington, D.C.

## The Bottom Line

The vast majority of men who undergo radical prostatectomy are cured. In a recent study of more than 1,300 men, cancer returned in 106 men. What made the difference? It’s not certain yet, but a recent Hopkins study suggests that weight gain and smoking may be key factors.

Men who gained five or more pounds near the time of their radical prostatectomy were twice as likely to have their cancer come back as men who maintained their weight.

Men who were still smoking a year after their surgery were also more than twice as likely, compared to men who had never smoked or who had kicked the habit, to have their cancer return.

## The Prostate Health Index Predicts Whose Cancer Will Progress

For years, Alan W. Partin, M.D., Ph.D., Director of the Brady Urological Institute, has been looking for a “better PSA.” This is because, even though PSA blood testing (along with the digital rectal exam – for more, see story on Page 6) has helped diagnose prostate cancer early in hundreds of thousands of men, it has also been responsible for a lot of unnecessary biopsies; also, confusion over how to interpret PSA has caused some cancers to be missed. “Presently, using PSA, we biopsy nearly five men to find one prostate cancer,” says Partin. “While biopsy is relatively safe and an effective way to diagnose prostate cancer, if we had a better test that could decrease the false positive biopsies from four out of five to, say, one out of two, that would be a great improvement.”

**“Presently, using PSA, we biopsy nearly five men to find one prostate cancer.”**

So strongly does Partin believe in the need for better tests for prostate cancer, that he has made this a priority at Hopkins. Several labs at the Brady and the Pathology Clinical Chemistry Department, with research led by Partin, Robert Getzenberg, Ph.D., Robert Veltri, M.D., Daniel Chan, Ph.D., and Lori Sokoll, Ph.D., have focused on testing molecules that have the potential to be more accurate than PSA. Some of this work has led to something called the Prostate Health Index (PHI). “It’s a mathematical equation,” says Partin, “that combines PSA, free-PSA and proPSA, to more accurately predict the need for a biopsy.” In a large trial, the PHI was calculated from blood tests of 1,372 men at eight different medical centers who underwent prostate biopsy; 430 of these men were found to have prostate cancer. “PHI

better predicted the presence of cancer than PSA or free-PSA alone,” says Partin. “In addition, PHI predicted the aggressiveness of the cancer with accuracy.”

Exactly what the PHI is sounds like something on a college prep test: “It’s the ratio of a PSA precursor protein to free PSA multiplied by the square root of the PSA score at diagnosis,” says Veltri, director of the Fisher Biorepository & Biomarker Laboratory at the Brady. He presented the results of another recent study at the annual meeting of the American Association for Cancer Research in Washington, D.C. The work is also due to be published in *Urology*. Veltri, Partin, Jonathan Epstein, M.D., and H. Ballentine Carter, M.D., studied 71 men who were in the Johns Hopkins Hospital Proactive Surveillance Program; 39 of these eventually developed an “unfavorable biopsy,” which means that either the Gleason grade had gotten higher, or the volume of cancer had increased. (In addition to the yearly biopsy, these patients also received a digital rectal exam twice a year.)

Combining PHI with DNA analysis of biopsy tissue, “we were able to identify 70 percent of men who could safely undergo active surveillance,” says Veltri. The PHI was higher in men who ended up having unfavorable biopsies; similarly, the amount of DNA in and near the biopsied areas where the cancer was found was significantly higher in men who were going to develop an unfavorable biopsy. Putting the information from the blood and tissue samples together made a big difference, even though at face value, the men seemed more alike than not, with similar-looking tumors, Gleason scores, and PSA levels.

“Our findings were slightly surprising,” Veltri adds. “The level of pro-PSA by itself was not able to predict who would develop an unfavorable biopsy. However, the PHI and DNA measurements were able to tell us which men were going to need treatment.” Two research fellows, Sumit Isharwal, M.D., and Dan V. Makarov, M.D., made important contributions to this investigation, and were instrumental in generating several other publications on this active surveillance research.



*Donald and Susan Sturm: Through their philanthropy, quietly committed to helping in the fight against prostate cancer.*

## Cancer-Free and Giving Back

For a lot of men, if all goes as it should – if prostate cancer is diagnosed early, when it is most curable, if it is treated effectively, and if the cancer never returns – prostate cancer is just an interlude. An unpleasant and scary one, to be sure, but something finite, to be remembered when it’s time to get that yearly follow-up PSA test; it’s a speed bump in the road, or, as surgeon Patrick C. Walsh, M.D., calls it, a “blip on the radar screen of your life.” A lot of men are cured of prostate cancer and then do their best to forget it ever happened. Life goes back to normal.

Then there are other men, equally cured, equally back to normal, who don’t forget. The Brady Institute has been blessed with more than its share of men like these, who want to do something to help fight this disease. Don Sturm is one of them. It’s been 10 years since he has been cancer-free. Sturm was not a stranger to prostate cancer; ever since his father had died of it, he says, “I was always aware of the risk that I could get it.” When he developed the disease at age 67, he

came to Hopkins to see Walsh, underwent a radical prostatectomy, “came through it in good shape,” and went back to his life in Colorado, where the former tax attorney oversees many business interests.

He did not tell many people about his bout with prostate cancer. But he and his wife, Susan, members of the Founders’ Circle, quietly committed themselves to helping find a cure.

Among the projects he has funded is research, led by Angelo De Marzo, M.D., Ph.D., and William Nelson, M.D., Ph.D. — both pioneers in discovering the root causes and tissue changes involved in prostate cancer’s earliest stages. With an award from the Sturm Foundation several years ago, these scientists studied a compound called PhIP; it appears when meat is cooked at very high temperatures, and this can cause cancer to begin, and to develop, in rats. “In this study,” says De Marzo, “we also found that PhIP causes inflammatory cells to enter into the prostate.” This work was among the first to show how diet, long suspected as a cause of prostate cancer, may work — by affecting inflammation in the prostate, which can make it more susceptible to developing cancer. These exciting findings resulted in several publications, new avenues of research to pursue, and a big grant from the Department of Defense for further study of PhIP and inflammation in prostate cancer. “The support from the Donald and Susan Sturm family allowed us to pursue several different research avenues, all related to the ultimate goal of preventing prostate cancer,” says Nelson.

Sturm, whose philanthropy also includes major support of the School of Law (which bears his name) at the University of Denver, believes he’s doing what he ought to do. “My wife and I feel that we need to give back to the society that gave us all the blessings that we have had and enjoy,” he says. He hopes that with sufficient funding, scientists will not only find a cure, but even better, that they will figure out a way in which “surgery may not be necessary,” where risks and genetic problems can be identified early on, and — perhaps through dietary changes, or medications — cancer can be warded off. “As far as prostate cancer is concerned, I think women have done a much better job in making people aware of breast cancer, and I think men need to do a better job in raising awareness of prostate cancer, because it’s just as prevalent.”

## Repeat Biopsy is the Key to Active Surveillance



*Epstein: Without repeat biopsy, cancer can be missed.*

You may be one of the lucky guys whose prostate cancer never needs to be treated. Then again, what if you choose active surveillance — monitoring the cancer closely for any sign of change — and the cancer develops more rapidly than anyone expected? You need

a yearly follow-up biopsy, says Jonathan I. Epstein, M.D., the Rose-Lee and Keith Reinhard Professor of Urologic Pathology. “Obviously, nobody wants to over-treat very low-risk prostate cancers,” he says, “but the repeat biopsy is essential to help detect cancers.” Hopkins is one of the few centers in

**Some aggressive cancers are so small that they don’t make enough PSA to set off any warning bells on a blood test.**

the world where repeat biopsies are a routine part of the active surveillance program.

In recent research, Epstein studied the surgical specimens of 48 men who were being closely monitored, but whose cancer eventually progressed and needed to be treated with radical prostatectomy. “We made three important findings,” he says. They are:

- Repeat biopsy can detect changes even in tiny bits of cancer. “We showed that we can follow men with very limited cancer on our active surveillance program, and when they show more advanced disease on repeat biopsy, most of them still have curable disease when they undergo radical prostatectomy.”
- Size doesn’t matter. Years ago, Epstein showed that very small tumors can be fairly aggressive. These cancers are so small that

they don’t make enough PSA to affect the level noticeably — which means a blood test alone would not set off any warning bells that the cancer had changed. “Without repeat biopsy, they may not have been detected until they were too advanced.”

- We know where the cancers are most likely to be overlooked. “The largest tumors in our study that were missed on active surveillance were in the anterior (front) part of the prostate,” says Epstein. “This would be missed, or difficult to sample, on a routine prostate biopsy and would be impossible to feel on a digital rectal exam.” Because of these findings, Epstein has modified the protocol for repeat biopsy in men undergoing active surveillance, to make sure this tricky part of the prostate gets adequately tested. Which means that “men on active surveillance can be monitored more effectively than ever.”

## “Bad Marriage” of Prostate Cancer Genes Linked to Male Hormones

Hopkins researchers have discovered that male hormones seem to be behind a bad marriage of two genes that’s found in nearly half of all prostate cancers. The finding, published in *Nature Genetics*, adds another brushstroke to a complicated picture, and may lead to new strategies to help prevent prostate cancer.

Cancer happens when something goes wrong in our genes; these mutations are called “acquired defects.” In this case, a gene named TMRSS2, which is controlled by male hormones, called androgens, breaks off from its original site in the cell nucleus and fuses with another gene, called ERG. The result is that prostate cancer cells respond to androgens by speeding up their growth. In previous research, led by Vasanth Yegnasubramanian, M.D., Ph.D., with William G. Nelson, M.D., Ph.D., Michael Haffner, M.D., and others, Hopkins scientists found that androgens use an “untan-

[continued on page 6]

[continued from page 5]

gling enzyme” to splice these genes.

“These types of defective fusions,” says Nelson, “have long been thought to be caused by errors in copying the genome when cells divide, or by mistakes in fixing the genome when it is damaged by cancer-causing chemicals, such as those found in foods or other environmental factors that are linked to cancer.” These new findings, he adds, “hint that the origin of the fusion events — which are so common in prostate cancer — may be the accidental breaking of TMPRSS2 upon activation by male hormones.”

## Digital Rectal Examination Can Predict Whether Cancer Will Come Back



Han: The exam is more valuable than ever.

Men hate it, and their doctors don't particularly like it, either, but they go through with it because it has saved countless lives, particularly when done yearly in combination with a PSA blood test. Now, it turns out that the digital rectal exami-

nation is more valuable than we realized. A new study has found that it can accurately predict whether a man's cancer will come back after surgery.

“We knew that men with a palpable prostate cancer” — a tumor that can be felt through the wall of the rectum during the exam — “have a higher likelihood of recurrence following surgery,” says Misop Han, M.D. But a recent study, led by Han, with Jeffrey Mullins, M.D., and Patrick C. Walsh, M.D., took this a step further. The team investigated whether the absence or extent

### The study included more than 4,100 men who had both digital rectal examination and radical prostatectomy by Walsh between 1983 and 2009.

of a palpable nodule before surgery (this is also known as clinical stage) could accurately predict long-term, cancer-free survival after surgery. The study included more than 4,100 men who had both the digital rectal examination and radical prostatectomy done by Walsh between 1983 and 2009.

“We found that most people do not die from prostate cancer after surgery,” says Han. Specifically, fewer than 4 percent of these men died from prostate cancer. They also discovered that men who had nonpalpable prostate cancer — cancer that is too small to be felt during the exam — before surgery (clinical stage T1c) lived significantly longer than those with palpable prostate cancer (clinical stage T2). “We found that, for men with palpable disease, the extent of the palpable cancer was directly associated with survival. Thus, having an accurate digital rectal examination is crucial in allowing doctors to give appropriate advice and guidance to their patients with prostate cancer.” The good news, Han adds, is that because more men are being screened for prostate cancer, more men are diagnosed with nonpalpable cancer.

## How Risky is Active Surveillance?

At Hopkins, the answer to the question in the headline is “not very.” This is because, ever since 1995, when H. Ballentine Carter, M.D., Patrick C. Walsh, M.D., and others began this program, the byword has been ultra-vigilance. Haunted by the similar-sounding philosophy of “watchful waiting” — promoted for years in Europe, it is as unlike what the Hopkins program is all about as night from day — the Brady urolo-

gists have bent over backwards working to make sure the program is as safe as can be.

Watchful waiting means, “sitting by and doing nothing until a man has symptoms and his cancer has spread beyond the curable point, then giving hormonal therapy and palliative treatment.” and nobody at Hopkins thinks that's a good idea. Active surveillance, or “expectant management,” is only possible because so much research in recent years — most of it done at Hopkins — has given doctors the tools to keep a very close watch on a man's cancer, so that at the least sign that it has changed, they can treat it with surgery or radiation when it is still curable.

*If there's a risk, why wait? Why not get that cancer out right away?* Immediate treatment is certainly a good option, and many men

**Today, many men are diagnosed with prostate cancer at such an early stage that immediate treatment is not necessary. This is why active surveillance is an option for some men.**

choose it because they want the peace of mind, and don't want to live with any uncertainty. The downside is that they put themselves through treatment that has side effects, a recovery time, the risk of incontinence and a small risk of incontinence.

And here's the kicker: They may not even need it. Today, many men are detected at such an early stage that immediate treatment is not necessary. This is why active surveillance is an option for some men. “An ideal candidate,” explains Carter, “is 65 years or older, and has a cancer with a very low risk of causing harm without treatment, based on prostate biopsy findings and a PSA history.” Although the cancer appears to be slow-growing, the doctors don't rely on assumptions; patients in the program undergo a digital rectal examination and PSA test every six months, and a follow-up biopsy once a year. (For more on the importance of the yearly biopsy, see story on Page 5.)

About 800 men have been enrolled in the program over the last 15 years. In a recent

study of 376 of these men, Carter and colleagues found that, at an average of six years after they entered the program, the cancer did progress in about 33 percent of these men, and treatment was recommended. Using the results of this study, the scientists were able to stratify men — who already were considered at very low risk of having their cancer progress — into risk categories:

- If a man's free PSA is greater than 15 percent and cancer is found in less than 35 percent of any biopsy core when he is diagnosed, his risk of reclassification (to a higher stage of cancer) at the first follow-up biopsy a year later is 8 percent.
- However, if a man's free PSA is less than 15 percent and cancer is found in 35 percent or more of any biopsy core at diagnosis, his risk of reclassification at the first follow-up biopsy is 29 percent.

"Furthermore, we were able to predict a man's probability of reclassification at four years after he enters the program using PSA density (PSAD, the ratio of PSA to prostate volume), and whether or not cancer is found on the first follow-up biopsy," Carter says. "For example, if a man's PSAD is below 0.08 and there was no cancer found on the first surveillance biopsy, his risk of reclassification four years after entering the program is 11 percent. On the other hand, if a man has a PSAD of 0.08 or higher, and his first follow-up biopsy shows very low-risk cancer that would not have prompted treatment, his risk of reclassification is 54 percent.

Thus, Carter adds, "finding any cancer on the first follow-up biopsy, coupled with PSAD, was predictive of the future risk of reclassification and a recommendation for treatment in this program." These findings were published in the *Journal of Urology*. "We believe this information could help individual patients make decisions about whether or not surveillance is right for them."

## The Bottom Line

The risk of cancer progression is higher if any cancer is found on the first follow-up biopsy, and a man's PSA density is 0.08 or higher.

## Hypertension Drugs May Speed, Strengthen Nerve Recovery after Surgery



*Burnett and Bivalacqua: Protecting the fragile network of blood vessels.*

Neuro-urologist Arthur L. Burnett knows, as a surgeon, that when he removes a cancerous prostate, he will inevitably place the extremely delicate nerves on either side of it at risk — even though he uses the "nerve-sparing" procedures pioneered by Patrick C. Walsh, M.D. For years, in laboratory and clinical studies, Burnett, M.D., M.B.A., the Patrick C. Walsh Distinguished Professor of Urology, has sought to blunt the shock of surgery. He has investigated neuroprotective agents that could act as therapeutic armor — shielding, strengthening, and even restoring these tiny nerves that are responsible for erection. Now, he is extending his scope of neuroprotection to the fragile network of blood vessels and chambers within the penis. Even though they're not directly traumatized by surgery, "these structures may degenerate or shrivel," he says, "and thus contribute to poor recovery of erectile function in some men after surgery."

Several years ago, investigators found that some drugs, designed to treat high blood pressure, also help make blood vessels stronger. Intrigued by these results, Burnett and colleagues began studying such agents (specifically, they're called "angiotensin II type 1 receptor antagonists") in rats with nerve injuries similar to those found in men after radical prostatectomy. They found

## A NEWLY DISCOVERED MOLECULAR CHAIN OF EVENTS Work Could Lead to New Therapies to Prevent Damage

Building on Arthur Burnett's years of research in neuroprotection and recovery of erectile function after radical prostatectomy, Trinity J. Bivalacqua M.D., Ph.D., has discovered a chemical chain of events that takes place when critical nerves around the prostate are injured. His research may lead to new drugs that can block these highly specific events, and prevent nerve damage. His work was published in the *Journal of Urology*.

Bivalacqua and colleagues have found that when the nerves surrounding the prostate are hurt, the body starts making more of a particular enzyme, called RhoA/ROCK (for "RhoA/Rho-kinase"). What happens next is a bad domino chain of nerve degeneration and death. "When RhoA/ROCK is increased in the penis and cavernous nerves after nerve injury" (the kind that occurs in prostatectomy), "erectile function is impaired," Bivalacqua says. Research of spinal cord damage has shown that the Rho pathway, activated by injury, prevents nerve axons (the long, spindly parts of nerves that send signals to other nerve cells or organs) from regrowing, or repairing themselves. When Bivalacqua and colleagues blocked RhoA/ROCK in animals with erectile dysfunction after cavernous nerve injury, these nerves fared noticeably better. "We saw nerve regeneration and protection of the blood vessels of the penis, resulting in the restoration of erectile function." He believes that understanding this RhoA/ROCK signaling cascade, and being able to block it, will lead to new strategies for treating erectile dysfunction — or, better yet, helping to prevent it.

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[continued from page 7]

that one of these drugs, called Irbesartan, not only speeds up the recovery of erections after surgery, but limits tissue scarring and nerve damage to the penis. The results have been so promising that Burnett began giving Irbesartan after surgery to his radical prostatectomy patients. "In preliminary results, we have observed measurably improved benefits in penile health and erection recovery," he says. He plans to begin a formal investigation of this nerve-strengthening therapy soon.

## Can We Stop PSA Testing 10 Years After Radical Prostatectomy?



Loeb: The vast majority remain cancer-free

The key word is "undetectable," and it's close to the heart of any man who has had a radical prostatectomy to treat prostate cancer. Once a year, he goes to the doctor, gets a blood test, crosses his fingers, and waits to hear that word. Even though

he's getting a PSA test, his real hope is that there won't be any PSA to show up on the test. PSA is made by the prostate, and after surgery, when the prostate is gone, all PSA-making activity should be gone, as well.

If the PSA becomes detectable (and it's not due to a mistake by the lab, which can happen; this should be ruled out first), this is known as "biochemical progression." If it's going to happen, biochemical progression will most likely rear its head in the first few years after radical prostatectomy. Studies at Hopkins and elsewhere have shown that if the PSA remains undetectable for the first five years after surgery, it is unlikely — although still possible — that

later biochemical recurrence will occur.

So, what happens after 10 years? You've sweated it out for a decade. Are we done yet? This is a question that Stacy Loeb, M.D., Ashley Ross, M.D., Ph.D., and Patrick Walsh, M.D., were curious to answer. If a man's PSA remains undetectable for 10 years after radical prostatectomy, is he still at risk of recurrence? To find out, they studied the records of 1,593 men who underwent radical prostatectomy at Johns Hopkins, who had gone at least 10 years after surgery without recurrence.

**So, what happens after 10 years? You've sweated it out for a decade. Are we done yet?**

While the vast majority — 94 percent — of these men remained cancer-free, biochemical recurrence later occurred in 6 percent of these men, more than 10 years after their surgery. This is called "late biochemical recurrence." Note: This was more likely to be found in men who underwent surgery in the early years after PSA testing first became available, and in men whose cancer was more aggressive (involving the surgical margin, seminal vesicles, or lymph nodes). "The good news here is that these men did very well," says Loeb. "Of the men who did recur, by 20 years after surgery only eight developed metastatic disease, and none died from prostate cancer. This study shows that *if the PSA stays undetectable for 10 years after radical prostatectomy, there is an exceedingly low risk of later prostate cancer recurrence*. In the few cases where late recurrence did occur, there was a very low risk of the cancer spreading to the bone, and no one died from prostate cancer. In the future, we may be able to tell men that it is safe to stop or decrease the frequency of PSA testing if they have made it 10 years after surgery without recurrence."

One limitation of the study, Loeb notes, is that all of the radical prostatectomies were performed at a high-volume academic center, and the results may not apply to all centers. However, these findings are so encouraging, that, if confirmed, "annual PSA testing may be unnecessary after 10 years for men with a prostatectomy Gleason

score of 6 or lower, and/or those whose life expectancy is limited due to age or other health problems."

## The Bottom Line

No man with an undetectable PSA at 10 years died from prostate cancer within 20 years after radical prostatectomy. In this study, cancer returned in only 6 percent of men more than 10 years after radical prostatectomy. Of these men, by 20 years after surgery, only eight developed metastatic disease, and none died from prostate cancer.

**NEW TEST OFFERS INSIGHT:**

## Is My Cancer Potentially Life-Threatening?

H. Ballentine Carter, M.D., and colleagues at the Baltimore Longitudinal Study of Aging (BLSA) coined the term, "PSA velocity." It's a way of looking at PSA, not just at one isolated test or another, but at a series of tests, looking not only for changes in the numbers, but at how quickly these changes occur.

Studying blood samples taken over a period of decades from the same group of men, Carter watched what happened to men's PSA levels, years before prostate cancer was diagnosed. Even when the PSA level was low, he found, if it changed by more than 0.35 ng/ml per year, the man was at risk of developing life-threatening prostate cancer.

More recently, Carter and colleagues at the BLSA found a new way to examine PSA velocity (PSAV). This method, called "PSAV risk count," predicts a man's risk of developing life-threatening prostate cancer. To calculate this, they counted



the number of times that a man's PSAV exceeded the threshold value (this is similar to breaking the speed limit in a car); how many times, in other words, his rate of change in yearly PSA levels was higher than 0.4 ng/ml. For example, say a man has two PSAV measurements in a row. If his PSAV both times is less than 0.4 ng/ml a year, his risk count is zero. If only one of the two PSAV measurements exceeds 0.4 ng/ml a year, his risk count is 1, and if both PSAV measurements break the speed limit of 0.4 ng/ml a year, his risk count is 2.

This year, a multi-institutional team of investigators, led by Stacy Loeb, M.D., tested whether the PSAV risk count could help resolve some of the drawbacks associated with prostate cancer screening — namely, unnecessary biopsies and the overdiagnosis of insignificant prostate cancer. In men attending a large prostate cancer screening study led by William J. Catalona, a PSAV risk count of 2 (this would mean a man had PSAV measurements that were greater than 0.4 ng/ml, twice in a row) was associated with an eight-fold higher risk of developing prostate cancer, and a five-times-higher risk of having high-grade disease. “This study showed that, after statistically controlling for age and PSA, the PSAV risk count dramatically improved the ability to predict high-grade prostate cancer,” says Loeb.

**“The PSAV risk count dramatically improved the ability to predict high-grade prostate cancer.”**

Having multiple PSA tests is essential, she adds, so that a man can develop a PSA history. “When we examine the changes in PSA levels over time, it tells us much more than we can learn from just one PSA measurement. In our study, men with sustained rises in PSA, or a PSAV risk count of 2, were substantially more likely to have prostate cancer, and particularly, to develop life-threatening disease. If 0.4 ng/ml a year is the ‘speed limit,’ then breaking it on multiple occasions carries greater risk. Compared to traditional PSA screening, this

PSAV risk count concept may be useful to reduce the number of unnecessary prostate biopsies and the diagnosis of the slow-growing, fairly benign prostate cancer that may not need to be treated.”

## Saving Lives with PSA Screening

Recently, a large trial in Europe showed that PSA-based screening reduces the number of deaths from prostate cancer by at least 20 percent. This was a landmark, the first randomized study to prove definitively that PSA screening saves lives.

However, this study, the European Randomized Trial of Screening for Prostate Cancer, reported that at nine years, 1,410 men needed to be screened and 48 treated to prevent just one prostate cancer death. Jumping to conclusions here may be a bit hasty, says Stacy Loeb, M.D., “because nine years is too early to look at prostate cancer deaths. Also, everyone agrees that men who are unlikely to live at least 10 years should not undergo PSA screening, or be put through aggressive treatments.”

Investigators from Hopkins, the National Institute on Aging, and Northwestern University organized a multi-institutional collaboration to determine how these numbers would change over time. Based on data from the European trial, they built a mathematical model to look at death from prostate cancer up to 12 years of follow-up.

“It became clear that as time went on, there was an even greater difference in the rates of prostate cancer death between the men who were screened, and the men who did not have regular screening,” says Loeb, the study's lead author. “Further, by 12 years, only 503 needed to be screened and 18 men treated to prevent one prostate cancer death.”

For breast cancer, she adds, “10 women need to be screened and treated to save a life with mammography. It is great news for men and their families that we have such an effective way to identify prostate cancer at a curable stage.”

### CANCER/TESTIS ANTIGENS:

## Helping Tell the Good Cancers From the Bad

As their name suggests, certain proteins called Cancer/Testis Antigens (CTAs) are made in the testicles; they're also expressed in several types of cancer, including prostate cancer. “CTAs are particularly interesting,” says Research Director Robert H. Getzenberg, Ph.D., “because they are expressed in different ways at various stages in a given cancer. This means that they have the potential to be biomarkers for diagnosing a cancer, as well as helping to predict how aggressive it will be.”

**“We believe that these differing patterns make a gene signature that may help in prostate cancer prognosis and early detection of advanced disease.”**

Fortunately, with the use of PSA testing and screening for prostate cancer, most men are diagnosed when their cancer is at a curable stage, and their cancer is considered “good,” adds Getzenberg, the Donald S. Coffey Professor of Urology. Even so, in some men, cancer returns, and “there is no good way of predicting who is at risk of disease recurrence.” Getzenberg and colleagues recently completed a systematic analysis of CTA expression in prostate cancer, and have identified several CTAs that are “stage-specific,” in other words, some are made by cancer that is confined within the prostate, and others are highly specific to advanced disease that has spread to distant locations. “We believe that these differing patterns make a gene signature that may help in prostate cancer prognosis and early detection of advanced disease.” Getzenberg and colleagues have developed a highly specific and quantitative assay for this gene signature, and are working to determine its ability to tell the good cancers from the bad.

## The Brady Is Named an O'Brien Research Center

George M. O'Brien was a Congressman from Illinois who died of prostate cancer; in 1987, the National Institutes of Health established specialized research centers in his name, and this year, the Brady Urological Institute became one of them. The Hopkins O'Brien Center, awarded a multi-million dollar grant from the National Institute of Diabetes, Digestive and Kidney Diseases, will study novel translational approaches for benign prostatic hyperplasia (BPH) and lower urinary tract symptoms in men. The Center will focus on three main projects:

- Exploring the role of inflammation in lower urinary tract symptoms. Inflammation is known to play a central role in prostate diseases, and this project, headed by Elizabeth Platz, Sc.D., M.P.H., will examine specific inflammatory pathways, and look for new approaches to treatment.
- Studying a novel biomarker. A protein found in the bloodstream may help doctors with early identification of more severe BPH and lower urinary tract symptoms. The study of this marker, called JM-27, or PAGE-4, will be headed by Robert H. Getzenberg, Ph.D., Director of Research, and the Donald S. Coffey Professor of Urology.
- Looking for genetic signatures associated with lower urinary tract symptoms. This project, the first of its kind, will be led by William Isaacs, Ph.D.

In addition to these projects, this Center will provide funds for pilot projects by scientists from Hopkins and the University of Maryland.

## Understanding the Physics of Prostate Cancer

One of the fundamental mysteries of advanced prostate cancer is, why does it become resistant to hormonal therapy, and even to chemotherapy? Something happens to aggressive cancer; it learns to evolve quickly, to become a moving, hard-to-kill target. "When this happens," says Robert H. Getzenberg, Ph.D., the Brady's Research Director, "another anti-androgen or chemotherapy drug is not going to be the answer. Instead, we need to attack the mechanism through which cancer cells develop resistance, and increase their sensitivity to currently available agents." Brady scientists are doing this, in two major initiatives:

### Physical Sciences in Oncology Center:

In a multidisciplinary effort, working together with physicists and engineers from Princeton University, cancer biologists from the University of California – San Francisco, scientists from the Scripps Institute and the University of California-Santa Barbara, Getzenberg, along with Brady colleagues Robert Veltri, Robert Ikvov and Donald Coffey, has received a grant from the National Cancer Institute to support a Physical Sciences in Oncology Center.

**"This is the 'anti-silo' approach, bringing basic scientists from the non-medical research world to the study of prostate cancer."**

"This is an excellent example of one of the strengths of the Brady," says Getzenberg, the Donald S. Coffey Professor of Urology. "Scientists are often accused of working in their own little silos, and not collaborating with others. This is the 'anti-silo' approach, bringing basic scientists from the non-medical research world to the study of prostate cancer." Together, these scientists are concentrating on the nucleus, the "brain" of the cell, to understand the evolutionary ability of cancer cells. "Rearrangements in the

DNA, along with changes in the shape and texture of the nucleus, are hallmarks of cells that develop resistance," says Getzenberg. "Our goal is to understand this element of the process."

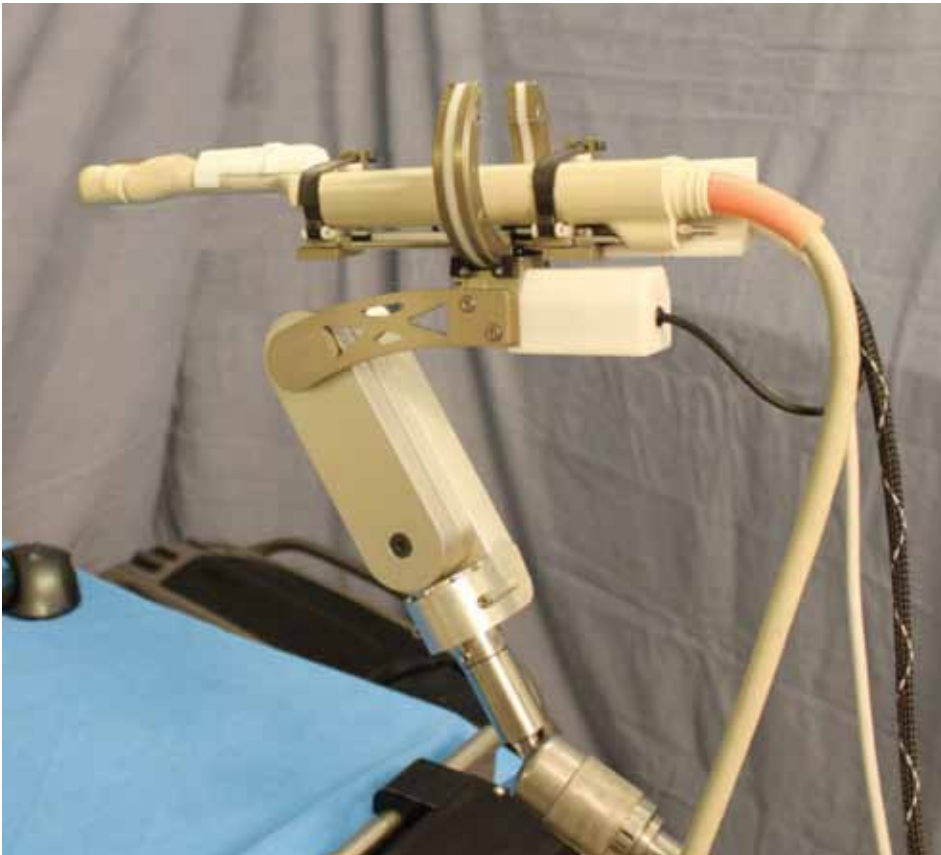
### Thermal-enhanced Metastatic Therapy

**(TEMT):** This is another interdisciplinary, multicenter project aimed at making aggressive prostate cancer easier to kill. Supported by Safeway/PCF, through money raised with many individual donations at the cash register, this program combines physics, chemistry, electrical engineering, material science and engineering, nanotechnology, cancer biology, and radiation oncology. The basic idea here, inspired by questions asked years ago by Donald S. Coffey, Ph.D., is that cancer cells become easier to kill when they are gently heated;

**How do you make aggressive, micrometastatic cancer cells easier to kill? Target them with tiny iron particles, then gently heat them up.**

even a few degrees higher than the regular body temperature is enough to make them vulnerable. Using tiny iron-containing particles that are heated with an alternating magnetic field, the Hopkins team is targeting cells that have metastasized, making them more sensitive to radiation and chemotherapy. This year, the team, including Coffey, Getzenberg, Theodore DeWeese, Robert Ikvov, Shawn Lupold and Prakash Kulkarni, has synthesized these nanoparticles and chemically modified them.

The goal is to hit only the cancer cells, and not the nearby healthy tissue; thus, the scientists are working on 'tagging' the nanoparticles with a chemical substance that will target them to the desired cells. The team has also designed and built a device that generates powerful fields, causing these particles to heat up, allowing for longer exposure of normal tissue to high-intensity radiation fields that only affect the nanoparticles. "Our tests with animal models were successful," says Getzenberg, "and we are now working with electrical engineers at Hopkins to test designs that



**New Robot-Guided Ultrasound Probe:** This is a new way of using an ultrasound probe, with the aid of a robot built at the Brady's Urology Robotics Laboratory. The robot is specially constructed to allow for prostate needle biopsy, as well as to provide live images of the prostate to guide the surgeon during robot-assisted laparoscopic radical prostatectomy. It was designed by a team that includes Dan Stoianovici, Felix Schäfer, Doru Petrisor, Chunwoo Kim, Bruce Trock, and Misop Han, and was supported in part by the National Cancer Institute, the Sidney Kimmel Comprehensive Cancer Center, and Hitachi Medical Systems America.

will be used in the clinic. If we are successful, this novel therapeutic approach would allow clinicians to trace micrometastatic tumors, and selectively target them to enhance their sensitivity to therapy." Also working on the TEMT project are scientists Ken Pienta, at the University of Michigan, and Martin Gleave, at the University of British Columbia, Canada.

## Will My Gleason Score Get Higher?

Maybe you're one of the lucky ones, with a low Gleason grade and a small tumor volume, and your prostate cancer is

considered "low-risk" enough that you are eligible for active surveillance. (For more on active surveillance, see story on Page 6.) You'll be closely watched. But wouldn't it be helpful to know if your Gleason score was likely to remain the same, or whether it might go up? Epidemiologist Bruce Trock, Ph.D., thinks so. He is the principal investigator on a grant from the National Cancer Institute to look for biomarkers that can help predict what will happen with a man's Gleason score. "Right now, the ability to safely offer active surveillance as an alternative to immediate treatment depends on the biopsy," he says, "and how well it can characterize the aggressiveness of the tumor in the entire prostate." With active surveillance as an option being chosen by more men who are diagnosed with a low Gleason grade, doctors need to know more, Trock adds: "We need to be able to predict

the possibility of unsuspected high-grade tumor for these men. This is an important clinical problem."

In this new study, scientists at Hopkins, the Mayo Clinic, Memorial Sloan Kettering Cancer Center, the Fred Hutchinson Cancer Research Center, and the UCLA Cancer Center, are evaluating more than 30 biomarkers, hoping that several of these, used together, will be able to predict the presence of high-grade tumor in men whose biopsies show only low-grade cancer. "If we are successful, this study could change the way treatment decisions are made in men with low-grade cancer on biopsy who are considering active surveillance," Trock notes, "and help reduce the over-treatment of prostate cancer."

*[continued on page 12]*

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### Prostate Cancer Pathology Resource Network

In other research, Trock is also the principal investigator of a grant from the Department of Defense's Prostate Cancer Research Program to explore a variety of biomarkers for several uses, including early detection of prostate cancer, determining individualized therapy, and predicting how aggressive cancer will be, or whether it needs to be treated at all. Although many biomarkers have been studied in recent years, none has become a major presence in any of these aspects of diagnosing and treating prostate cancer. One reason for this "lack of translation" to clinical use, says Trock, "is that results are often inconsistent among studies of the same biomarker." And this is because these results often come from fairly small, retrospective studies that use tissue samples that are not representative of the disease, and non-standardized methods. Also, he adds, scientists don't fully understand how the way tissue is handled and processed before it is analyzed can affect the biomarker findings.

**"This network...will speed the clinical translation of biomarker research, understanding of tumor biology and the impact of prostate cancer genetics on risk."**

The Department of Defense Prostate Cancer Pathology Resource Network, established with this grant, is a major step toward correcting these problems and advancing translation of biomarker research, Trock says. Johns Hopkins will lead a network of centers that will conduct research to define optimal, standardized protocols for important classes of biomarkers, and use these protocols to provide high-quality biospecimens. "This network will provide a tremendous resource for prostate cancer researchers, and will speed the clinical translation of biomarker research, under-

standing of tumor biology and the impact of prostate cancer genetics on risk."

## How Safe is a Prostate Biopsy?

It's considered a routine procedure, used to diagnose prostate cancer, and to monitor men in active surveillance. But new research at Hopkins suggests that at many hospitals, prostate biopsy may be slightly riskier than doctors realized. "This is an extremely common procedure," says urologist Edward Schaeffer, M.D., Ph.D. "But since the early 1990s, when it first came into widespread use, antibiotic-resistant bacteria have emerged as a menace in hospitals nationwide." Because of this, Schaeffer, along with urologists H. Ballentine Carter, M.D., and Stacy Loeb, M.D., recently wondered whether the procedure is as safe as it used to be.

**"We found that the rate of infectious complications after prostate biopsy has increased over time."**

To examine this question, the investigators looked at the rates of hospitalization for serious complications in male Medicare patients across the country who underwent prostate biopsy, and in similar patients who did not undergo biopsy. "Surprisingly, nearly 7 percent — almost three times as many as in the comparison group — of men who had a prostate biopsy were hospitalized within 30 days," says Schaeffer. After taking into account other risk factors, the investigators found that the increased hospitalizations in the biopsy group were due both to biopsy-related problems and to exacerbations of underlying medical conditions.

"We found that the rate of infectious complications after prostate biopsy has increased over time," Schaeffer adds. The scientists believe that drug-resistant bacteria may be driving some of these complications. "These results suggest that prostate biopsy is not

always a benign procedure, and this should be taken into account by patients and physicians before a man undergoes a biopsy.

"At Johns Hopkins, we take several measures to ensure that prostate biopsy is as safe as possible, and have a low rate of complications. The findings of this analysis were surprising to us." The next step, the investigators say, is to figure out how to make biopsies even safer, at Hopkins and elsewhere.

## Anti-Angiogenesis Drug Nears Clinical Development

It's not easy being a constantly growing cancer. For one thing, you need a lot of food, and your host body doesn't just hand it to you on a platter; you have to work for it. Think of any invading army, and the infrastructure needed to keep it going. Similarly, prostate cancer, on its lethal push toward metastasis, requires an ever-increasing blood supply, which serves as a highway for the supply trucks (in this case, nutrients and oxygen). The process of paving this road, making new blood vessels inside a cancer, is called tumor angiogenesis.

**It's not easy being a constantly growing cancer. For one thing, you need a lot of food, and your host body doesn't just hand it to you on a platter; you have to work for it.**

Over the last two decades, scientist John Isaacs, Ph.D., has made it his mission to stop this process — looking, in effect, for anything that might become an effective roadblock, and make it harder for the food supply to reach prostate cancer. He has found several in the form of "small molecule inhibitors." In collaboration with Active Biotech AB, his research group has identi-

fied a particularly promising, angiogenesis-inhibiting substance called tasquinimod. Based on his pre-clinical studies, tasquinimod has completed a randomized, placebo-controlled, double-blind Phase II trial, and moved a step closer to being available to patients everywhere. In this trial, 206 men in the U.S., Canada, and Sweden, with metastatic, hormone-resistant cancer (but no symptoms, such as pain), were given either 1 mg daily of oral tasquinimod, or a placebo. In the placebo group, 66 of the men had progression of their cancer, compared to only 31 percent of the men on tasquinimod. “The drug not only inhibited progression, but delayed it,” says Isaacs. “Based upon these results, tasquinimod will shortly enter Phase III FDA registration trials.”

## New Drug Makes Cancer Cells More Susceptible to Radiation Therapy

A new drug, developed after years of work by two Hopkins scientists, specifically targets prostate cancer cells, gets inside them, and sabotages their ability to repair DNA damage, so that they are more likely to be killed by radiation therapy.

### Idea One: Stop Cancer Cells from Repairing Themselves

The drug is a combination of two ideas, begun in separate labs by Theodore L. DeWeese, M.D., Professor and Chairman of Radiation Oncology and Molecular Radiation Sciences, and Shawn Lupold, Ph.D., the *Phyllis and Brian L. Harvey Scholar*. About seven years ago, DeWeese was the first to describe the use of a substance called a “small interfering RNA,” or siRNA, to hinder a prostate cancer cell’s ability to repair DNA damage. “An siRNA is a tiny molecule made up of ribonucleic acid (RNA), arranged in a very precise and specific manner,” DeWeese explains. Once

they’re made, siRNAs can be put into cells to target another type of RNA in the cell, called messenger RNA; this is the molecule that serves as the cell’s “how-to guide” for making proteins, including proteins that repair DNA damage from radiation.

**Cancer cells are like roaches; they can hide anywhere, and even though they don’t scurry away when you turn on the light, it’s similarly hard to spot and kill them all.**

“It’s fascinating to see how the siRNA and messenger RNA work together; they link up tightly and specifically, like a zipper,” says DeWeese. “Together, they tell the cells to destroy the messenger RNA, and this stops the machinery from repairing DNA damage.” In published work, DeWeese’s group reported that putting these siRNAs into prostate cancer cells made them about twice as sensitive to radiation.

### Idea Two: Give Cancer Cells Nowhere to Hide

Cancer cells are like roaches; they can hide anywhere, and even though they don’t scurry away when you turn on the light, it’s similarly hard to spot and kill them all. If only we could shine a spotlight on them, so they had nowhere to hide. Lupold has done this, in a highly sophisticated way, at the molecular level. Several years ago, Lupold began developing and testing molecules called aptamers for cancer cells. Aptamers are also small bits of RNA, but unlike the siRNAs DeWeese makes, Lupold’s molecules act as targeting beacons — tiny spotlights — that seek out cancer cells and stick to targets on their surface. Think of paintball, on a tiny scale. Aptamers don’t treat the cancer, but they target the heck out of it, so that other forms of treatment can aim and fire at these cells only, and minimize damage to normal tissue. Lupold began working on these aptamers when he was a student in the lab of Donald S. Coffey, Ph.D., the Brady’s

renowned research director for many years. Lupold, DeWeese notes, “was the first to show that his aptamers would specifically bind to the PSMA (prostate-specific membrane antigen) on the surface of most prostate cancer cells, and do so in manner that would carry the aptamer inside the cancer cells. His aptamers are so good at binding PSMA that multiple investigators around the world have been using them in their own research, as a way to very specifically target and deliver agents to and inside prostate cancer cells and tumors.”

A few years ago DeWeese and Lupold joined forces to make and test a new drug that combines an aptamer with siRNA drug. They have done this, with promising results. “The result is prostate-specific,” says Lupold, “making these cells much more sensitive to radiation.” Also lending their expertise to this project are scientists Xiohua Ni, Ph.D., and Yonggang Zhang, M.D. They have shown that the combined drug can be made successfully, that it can target PSMA on prostate cancer cells, that siRNA can be sent like a PSMA-

**Think of paintball, on a tiny scale. Aptamers don’t treat the cancer, but they target the heck out of it, so that other forms of treatment can aim and fire at these cells only, and minimize damage to normal tissue.**

seeking missile to the cell and that, once it gets inside, that it can disrupt the DNA damage-control system. Most recently, in mice, the team has demonstrated that the combined drug makes the prostate cancer cells dramatically more sensitive to radiation, and that it provides substantial, long-term control of human prostate tumors. “Also,” says DeWeese, “treatment of human prostate tissue with the new aptamer-siRNA agents, immediately after radical prostatectomy, results in a notable decrease in DNA repair proteins.” Thus, the

[continued on page 14]

[continued from page 13]

drug is working well both in pre-clinical models and in clinical samples.

Where do they go from here? DeWeese and Lupold are excited about their results, and are moving toward a clinical trial of their drug. They are also conducting further tests in animals to see how well the drug targets prostate cancer cells when it is administered intravenously, with the hope that this will prove a new method of sensitizing metastatic prostate cancer cells to both chemotherapy and radiation.

## Molecular Tools Help Tell Deadly Cancer from Its Milder Kin

Robert Getzenberg, Ph.D., Director of Research, calls it “assembling a set of tools.” He’s talking about new biomarkers to help doctors diagnose prostate cancer and also predict its course — tell whether it’s likely to be aggressive, or whether its growth will be slower and more benign. A new protein looks to be a promising addition to the toolbox.

**“The goal is to help determine which men have prostate cancer with lethal potential.”**

It’s called Cyr61 (for cysteine-rich angiogenic inducer 61), and it is involved in the cell’s connection to its environment. With a team of scientists, including pathologist George Netto, epidemiologist Elizabeth Platz, and Katherine D’Antonio, a graduate student, Getzenberg examined the link between Cyr61 and recurrence of cancer. They looked at “staining intensity,” or how much of the protein showed up in stained tissue samples of 558 men who were treated surgically for clinically localized prostate cancer.



*Honorary degree: Patrick C. Walsh, M.D., was awarded the Doctor Honoris Causa by the Medical School of the University of Athens for his contributions to the field of prostate cancer research.*

“Taking into account age, pathological stage and grade, PSA concentration, and other factors, men with the highest level of staining intensity in their cancer were 56 percent less likely to have a recurrence of cancer than men with a lower staining intensity,” says Getzenberg, the Donald S. Coffey Professor of Urology. “Therefore, high Cyr61 staining intensity within the prostate cancer was associated with a lower risk of recurrence after treatment.” Although more work is needed, Getzenberg believes this test and others, used alone or in combination, can help with “risk stratification. The goal is to help determine which men have prostate cancer with lethal potential, and which have very low-risk cancer, who may be more appropriately treated with a program such as our Proactive Surveillance.”

The team’s findings are due to be published in the journal, *Clinical Cancer Research*.

### MAKING A GIFT

If you are interested in making a gift to support prostate cancer research, please call the Development Office at (410) 955-8434, or send an email to Shabina Bahl at: [shabina@jhu.edu](mailto:shabina@jhu.edu)

**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>

*If you do not wish to receive this newsletter please write to us at The James Buchanan Brady Urological Institute, The Johns Hopkins Medical Institutions, Baltimore, MD 21287-2101.*

## THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND

## Here's Some of the Exciting Research You Have Helped Support

It's been a remarkable five years since we launched the Patrick C. Walsh Prostate Cancer Research Fund. We welcomed every scientist at Johns Hopkins, in every department, to compete for a grant; our only requirement was that they had a good idea that could help us defeat prostate cancer. This year, we awarded more than \$1 million to 13 recipients — talented scientists all, and blessed with the kind of creative thinking that is going to help make life better for men with prostate cancer, and their families. For more on this Fund, see story on Page 1.

**Peter N. Devreotes**, Ph.D.  
*Department of Cell Biology and Anatomy*

**Shawn Lupold**, Ph.D.  
*Phyllis and Brian L. Harvey Scholar  
Department of Urology*

**Elizabeth Platz**, Sc.D., M.P.H.  
*Beth W. and A. Ross Myers Scholar  
Department of Epidemiology  
School of Public Health*

**Ronald Rodriguez**, M.D., Ph.D.  
*R. Christian B. Evensen Scholar  
Departments of Urology, Medical Oncology,  
and Cellular and Molecular Medicine*

cells has proven enough to delay significantly the growth of tumors in mice. In other studies, when these cells were targeted at specific proteins, they attacked them with gusto, and just a few were able to produce a significant effect. "We suspect that these results will carry over to prostate cancer," notes Drake. Next, his lab will see whether IL-producing lymphocytes can actually stop the growth of prostate cancer in mice.

What Drake really wants to know now is whether IL-17-producing cells already exist in the prostates of men with cancer. He plans to look for them in surgical specimens of men who have undergone radical prostatectomy. And if he finds them, "then it might be possible to specifically boost this population of IL-17 secreting lymphocytes," with the goal of creating a more powerful immune response to prostate cancer. And if he can do this, he believes, one day it may be possible "to help men with the disease live longer without the side effects of hormonal or chemotherapy."

## THE 2009–2010 AWARDEES

**Charles Drake**, M.D., Ph.D.  
*Nancy and Jim O'Neal Scholar  
Department of Oncology*

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

**Prakash Kulkarni**, Ph.D.  
*Irene and Bernard L. Schwartz Scholar  
Department of Urology*

**Jun Luo**, Ph.D.  
*Carolyn and Bill Stutt Scholar  
Department of Urology*

**Alan Meeker**, Ph.D.  
*Virginia and Warren Schwerin Scholar  
Departments of Pathology and Urology*

**David Shortle**, M.D., Ph.D.  
*Department of Biological Chemistry*

**Mario Eisenberger**, M.D.  
*Departments of Oncology and Urology*

**Paula Hurley**, Ph.D.  
*Department of Urology*

Receiving their second year of funding are these  
2008–2009 AWARDEES

**Angelo M. De Marzo**, M.D., Ph.D.  
*The Peter Jay Sharp Foundation Scholar  
Department of Pathology*

### Immune Therapy: Chemical Shows Promise as New Cancer-Killing Weapon

Charles Drake, M.D., Ph.D., wasn't too impressed with a particular kind of chemical, called IL-17, made by immune cells in the prostate. His lab had been studying it, and IL-17, a cytokine made by immune cells called lymphocytes, didn't seem like much of a fighter; it couldn't kill target cells in specially designed assays. Nonetheless, "we wanted to test what these cells did in the body," says Drake, the *Nancy and Jim O'Neal Scholar*. So, in difficult, time-consuming work, they made up a batch of IL-17-secreting lymphocytes, put them into animals — and were amazed at the results.

"To our surprise, we found that immune cells that make IL-17 are more active than other immune cells," says Drake. "They seem to move more widely throughout the body, and to do a better job of killing their targets." Like any good warrior, these IL-17-making cells also turned out to be adept at more than one weapon. "We found that these cells could change after seeing their targets — although they originally made IL-17, they could switch to making another cytokine known as interferon gamma. This is very important, since the production of interferon gamma is associated with the ability of these cells to kill."

Just a small dose of these IL-17-secreting

### Hevin, the Missing Gene that Might Help Stop Cancer

What does fetal development have to do with cancer? More than you might think. Although one process is healthy and good, and the other is harmful, both involve intense periods of growth. The big difference is that in cancer, certain switches that should be able to stop cells from dividing either aren't there, or are not working as they should. And, in cancer — when it starts, and also as it progresses — some pathways that were designed to do their main work before birth are reactivated.

One of these is a switch called Hevin. It's a gene that is "dynamically regulated during prostate development, but it's disrupted in prostate cancer," says Paula Hurley, Ph.D. She is interested in learning more about Hevin because it can help keep tumors from forming, "and in many forms of cancer, it is significantly reduced or lost." Hurley is working to trace the molecular pathways that Hevin uses to

[continued on page 16]

## THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND

[continued from page 15]

stop cancers from forming, and to find out whether the shutdown of this gene makes a man more susceptible to prostate cancer forming and advancing. “Understanding the molecular underpinnings contributing to prostate cancer will help us develop targeted therapies,” she says, drugs specially designed to work with these pathways to stop prostate cancer in its tracks.

### Family History and Prostate Cancer: New Technology Speeds Up the Hunt for Genes

They are a bad threesome, the risk factors for prostate cancer: Age, race, and family history. It is in large part due to William Isaacs, Ph.D., the *Dr. and Mrs. Peter S. Bing Scholar*, that we know as much as we do about this third risk. Two decades ago, when Isaacs, who is also the William Thomas Gerrard, Mario Anthony Duhon and Jennifer and John Chalsty Professor of Urology, began looking for proof that prostate cancer runs in families, most doctors thought prostate cancer was just an incredibly common disease in older men. Over years of groundbreaking work, he and colleagues have found certain genes and genetic variations — which can be inherited from either the mother or father — that can make a man more susceptible to developing prostate cancer. When they first started, their work was so labor-intensive and painstaking that Isaacs may have wondered why he’d gotten himself into such an ambitious undertaking.

Things are much different now. “The technology to sequence the human genome has gotten dramatically better and less expensive, even over the past year,” says Isaacs. This new technology is called “next gen sequencing,” and with it, Isaacs believes, his lab can make rapid progress in identifying and characterizing the inherited genes that could make a man, and his sons and grandsons, prone to developing prostate cancer. “We are in the process of sequencing the complete coding portion of the DNA in patients with a strong family history of developing aggressive prostate cancer at a young age,” he says. “These are the men who need to know as soon as

possible that they are at risk, and who will benefit most from early disease screening, diagnosis and treatment.”

### Why Does Hormonal Therapy Work So Well for Some Men?



Eisenberger: Mystery in advanced cancer

What is going on here? Something is mystifying to Mario Eisenberger, M.D., the R. Dale Hughes Professor of Oncology and Urology, and he wants to understand what’s happening, because he thinks the answer will bring help to men

who desperately need it.

The puzzle has to do with advanced cancer. When prostate cancer is confined to the prostate, the best solution is a mechanical one — figure out the perimeter of the disease, and remove all cancer inside it. That becomes more difficult as the cancer spreads, and when it has set up outposts at distant sites, there is no way to say, “This area has cancer and I’m going to remove it,” because nobody knows exactly where all the cancer cells are. This brings us to Plan B: Finding something that prostate cancer cells have, and targeting that specifically.

**Some men have prostate cancer that is particularly susceptible to hormonal therapy, and their disease goes into remission for many years.**

The most obvious thing that prostate cancer cells have is androgen receptors; the prostate’s growth, from before birth, is driven by the presence of male hormones, called androgens. One way to shut down advanced cancer is to cut off its supply of these hormones; this is called “androgen deprivation therapy,” or hormonal therapy. In most

men, when the hormones are gone, the PSA goes way down, there’s an improvement in symptoms, such as pain, and the cancer shrinks — but this remission doesn’t last. “Unfortunately, most patients progress,” says Eisenberger, “anywhere from around 18 months to four years.” In a few men, he notes, androgen deprivation therapy doesn’t work at all. “In these men, the disease progresses rapidly, and becomes fatal.”

But then there’s a third group. Not nearly as big as the first group, but Eisenberger has seen more of them in recent years. “These are men with advanced metastatic disease who respond dramatically to androgen deprivation therapy. Their disease seems to go away, and their remission is durable, lasting years longer than that of most men.”

These men, Eisenberger suspects, have distinctly different cancers — subtle genetic variations, or specific changes in their DNA that affect how they metabolize androgens — that somehow make them more susceptible to hormonal therapy. Working with a multidisciplinary team of Hopkins scientists, including Angelo De Marzo, Srinivasan Yegnasubramanian, Elizabeth Platz, Daniel Kejzman, Michael Carducci, Samuel Denmeade, Bruce Trock, Alan Partin, William Nelson, and Patrick Walsh, Eisenberger hopes to identify the secrets that give these men years longer than others who would seem to be in exactly the same situation.

“We will start by characterizing these three groups of men who develop metastatic disease after radical prostatectomy,” says Eisenberger, “their clinical, pathologic, and demographic factors,” looking for anything that sets them apart. They will look at the genetic makeup of these men, and look for possible new targets for treatment and, also, for ways to predict men whose disease is unlikely to respond to hormonal therapy, who can be spared its side effects, and directed to chemotherapy and other approaches.

### New Way to Target Prostate Cancer?

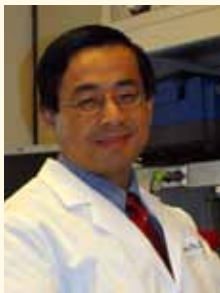
It is the elusive brass ring for scientists seeking better ways to kill prostate cancer — a drug that kills only the cancerous cells, but leaves normal cells unscathed. “Creating drugs



that do this is very difficult,” says Prakash Kulkarni, Ph.D., the *Irene and Bernard L. Schwartz Scholar*. “Certain genes that are over-expressed in cancer cells are usually identical to those made in normal cells; or, if they have mutated, the difference is very subtle.” But one, called PAGE4 (for “P. Antigen Family Member 4), a Cancer/Testis Antigen, is made only by the prostate and the testis. It is “remarkably prostate-specific,” Kulkarni says, and it is present in prostate cancer.

Kulkarni believes that PAGE4 plays an important role in the formation of prostate cancer, and that it represents an ideal target for killing cancerous cells. He and colleagues are studying PAGE4 in both prostate cancer that responds to hormones, as well as in aggressive disease that does not respond to hormones. They are also working to develop a specific assay that will allow them to search for small molecules specific for PAGE4 in libraries of chemical compounds, studying thousands of cells at once. The goal, Kulkarni says, is to develop a drug that will help thwart PAGE4. “This could have a significant impact on the management of prostate cancer.”

### New Findings May Explain Why Prostate Cancer Hits African American Men the Hardest



Luo: Race affects prostate cancer

men get, the kind that Asian men get, and the kind that affects black men. And in general, American men of African descent seem to have it the worst: “Prostate cancers diagnosed in African American men are more likely to progress to an advanced stage even after definitive treatment,” says Jun Luo, Ph.D., the *Carolyn and Bill Stutt Scholar*, “and these men are most

likely to die of prostate cancer.” Luo is interested in pinpointing and characterizing the tiny differences in the molecular makeup of men of different ancestries. “This line of research,” he believes, “may help us uncover the biological processes that affect the development of cancer, and determine how severe that disease will be. Most importantly, it may help us find new ways to save lives from prostate cancer.”

He has discovered an important new contender in the interplay between race and cancer — an enzyme called PLA2G7, which fights inflammation. In recent years, investigators at Hopkins have demonstrated that inflammation is involved in cancer’s very earliest stages; inflammation is thought to progress to precancerous changes, which ultimately become cancerous. Lower-than-normal levels of this anti-inflammatory enzyme are known to be a factor in cardiovascular disease. In exploratory studies, Luo found that it’s a worse culprit than scientists suspected: “PLA2G7 is linked to prostate cancer progression in African American men.” Here are some other key facts Luo has discovered about this enzyme:

- In blood and tissue samples of men with prostate cancer, PLA2G7 levels are generally lower in African American men than in men of European descent;
- Lower production of PLA2G7 is more likely to be found in men with advanced prostate cancer; and
- African American men are more likely than others to inherit a particular variant of the PLA2G7 gene that is linked to a recurrence in cancer after prostatectomy.

Luo believes the connection between PLA2G7, these genetic variants and cancer — and worse, aggressive cancer — is so strong, that his studies may lead to new markers for aggressive cancer, and even to race-specific tests. “We are looking to see whether PLA2G7 can differentiate between aggressive and non-aggressive prostate cancer,” he says, “and whether we can pinpoint the genetic variants of PLA2G7 that make cancer more likely to progress, with the goal of better, earlier detection and treatment of potentially lethal prostate cancer.” Also, what he learns about PLA2G7 could lead to new avenues of treatment — for example, drugs that boost this enzyme, fight inflammation, and slow or prevent the progression of prostate cancer.

## The Bottom Line

African American men are most likely to develop aggressive prostate cancer, and to die from it. Luo has discovered that the loss of an enzyme, called PLA2G7, is largely to blame. His findings are so conclusive that they may lead to new, race-specific tests for potentially lethal cancer.

### Needed: A Better Animal Model for Aggressive Cancer



Meeker: Rats get more aggressive cancer.

When it comes to prostate cancer, men are much more like rats than mice. Rats, like men, spontaneously develop the disease. As it advances, the cancer changes in rats, as it does in men; it grows unstable and aggressive, becomes more likely to spread

throughout the body, and to come back after treatment.

Although they’ve gathered many pieces of the puzzle, scientists still don’t know all the reasons why some men are fortunate enough to develop a mild, slow-growing form of prostate cancer, while others have the dangerous kind, the one that’s most likely to defy treatment. Identifying which type of cancer an individual patient has would help men and their doctors determine the best course of treatment.

One big roadblock in learning more about the complicated, advanced cancer that can so easily morph into different forms — each resistant and susceptible in its own way to various drugs designed to kill it — is the lack of a good animal model. Scientists trying to save the lives of men with prostate cancer have long studied the disease in mice, but there are limits, says Alan Meeker, Ph.D., the *Virginia and Warren Schwerin Scholar*. “None of the mouse forms satisfactorily

[continued on page 18]

## THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND

[continued from page 17]

mimics the most common lethal forms of metastatic human prostate cancer.” He believes this is because it takes several bad things happening in the genes — several different mutations — for the disease to progress in men, “but mouse models rely on the introduction of only one or two well-defined genetic changes.” Also, mouse models of cancer aren’t as unstable, and their disease tends to progress more slowly, or not at all.

On the other hand, rats — whose physiology more closely mimics human physiology than that of mice — have the potential to become excellent models of human prostate cancer, Meeker notes. However, at present “only one genetically engineered rat model exists, and this model is based on activating a protein that comes from a virus that has never been linked to human prostate cancer,” he adds. This rat model’s usefulness is limited, mainly because “it does not recapitulate important features of late-stage human prostate cancer.”

Meeker hopes to change this, by developing innovative models that more closely mimic key features of human prostate cancer. He is developing a rat model by recreating the same molecular changes that probably cause aggressive disease to begin and progress in men. The result of his work will not only help scientists learn more about the worst kind of prostate cancer, but will help them test new drugs aimed at these men who need it most.

## The Bottom Line

Nearly all animal studies of prostate cancer are done in mice. Yet mice don’t develop the aggressive, unstable disease that causes such harm in men. Rats, on the other hand, like men, naturally develop the kind of prostate cancer that can be fatal. They have the potential to become excellent models of this disease, and to test new forms of treatment.

## Instead of Targeting Cancer’s Growth, How About Messing Up Its Metabolism?

Scientists have long known that when a normal cell becomes cancerous, certain genes — the ones that make sure cells grow in an orderly way — get out of whack. But much later on, trouble finds other genes, too; these aren’t involved in *making* cancer, but in *driving* it, and these genes can become mutated, deleted, or duplicated.

At Hopkins and elsewhere, investigators have dedicated their lives to identifying the aberrant genes that cause cancer, with the hope that they can target these genes, and stop the disease. But David Shortle, M.D., Ph.D., and Alan Meeker, Ph.D., are taking a different tack: What if, they wonder, instead of focusing on controlling cell growth, they could target the central metabolism in cancer cells? It takes hundreds of reactions, driven by enzymes, to generate the chemical energy and small molecules that cells need to survive and keep on growing.

Scientists already know quite a lot of the biochemistry of cancer cells; for instance, “they’ve documented a variety of metabolic abnormalities and deficiencies, plus heightened sensitivities to inhibitors of metabolism,” says Shortle. “Numerous cancer researchers have commented on these observations as possible avenues for new forms of chemotherapy. As cancer cells experience increasing physiologic stress as a result of these alterations, they become vulnerable to killing by additional stresses, induced with metabolic inhibitors.”

Metabolic inhibitors are drugs or agents that throw the proverbial monkey wrench in the clockwork of a cell; Shortle and Meeker believe that using several inhibitors — each one blocking a different reaction in a cell’s handling of the energy it needs to keep going — in combinations, at very low, non-toxic levels, will cause metabolism to fail in cancer cells, but not normal cells. “Our logic is that random genetic events, especially deletions and duplications of parts of chromosomes, have altered both the amounts of enzymes required for metabolism and the intricate feedback mechanisms responsible for their control,” Shortle says. “Because this network of reactions is so tightly intercon-

nected, if we partially inhibit multiple reactions, it should be much more harmful to cancer cells than to normal cells with these mechanisms intact.”

## Creative, Never Done Before, Cutting Edge: All in a Day’s Work

Ron Rodriguez, M.D., Ph.D., the *R. Christian B. Evensen Scholar*, and Shawn Lupold, Ph.D., the *Phyllis and Brian L. Harvey Scholar*, are combining the forces of their labs and creativity to pursue prostate cancer from multiple fronts. Here’s some of what they have accomplished recently:

**Giving cancer a lethal cold:** In work published in *Cancer Research*, Lupold, Rodriguez, and post doctoral fellow Ping Wu have managed in a few years what others have been trying to do for a decade. It’s called “viral retargeting.” In this case, they used the adenovirus, a pesky bug that produces common cold symptoms. An adenovirus naturally attacks epithelial cells, which are in the tissue that lines structures throughout the body (this makes sense, that a virus that makes your nose run would attack the membrane in the nostrils, and similar tissue elsewhere). The virus attaches to specific receptors on epithelial cells, by means of a fiber protein that lives on its surface (think of Spiderman shooting out sticky string). Using a novel adenovirus-library approach, Lupold and Rodriguez screened millions of slightly-modified viruses to identify one that, instead of being drawn to all epithelial cells, specifically targets PSMA (prostate-specific membrane antigen), found only on the surface of prostate cells.

“This opens the road to developing better treatments for prostate cancer,” says Lupold, “which can be given intravenously, without losing more than 99 percent of the virus to the liver and immune system; this has been a big problem in the past.”

**A virus/hormonal therapy/radiation combo:** In separate work, Rodriguez and Lupold have engineered a virus to kill prostate cancer cells when given with an oral anti-androgen medication. “To our

knowledge, this is the first example of a virus that is regulated by an anti-androgen,” says Rodriguez. “This particular virus is most active only in the presence of the oral anti-androgen and radiation together. “The idea with this particular virus is that it will serve as a “biological sensitizer,” making the cancer more vulnerable to radiation, and also making the radiation much more effective. “We are also developing the virus in a way that would activate the immune system against the tumor, and this may help prevent early spread of the disease.”

**Clinical trials:** Two clinical trials are under way with treatments the Rodriguez lab has developed. One uses valproic acid, an anti-seizure drug that has been around for many years. The drug inhibits a chemical called histone deacetylase, and this slows the growth of prostate cancer. The scientists believe it can help slow down the progression of prostate cancer in men whose cancer has returned after radical prostatectomy. The other trial involves another fusion of treatments, cryotherapy plus immunotherapy. Cryotherapy, or cryoablation, involves freezing the prostate. As a treatment by itself, it has not been shown to cure advanced prostate cancer. However, when an immune-boosting drug called cyclophosphamide is given alongside, it can help strengthen the body’s ability to fight the cancer. Rodriguez and Lupold envision adding several other immune-boosters to the approach, “with the goal of ultimately reversing established metastatic disease,” says Rodriguez. “In our animal models, such multi-armed combinations have been able to reverse metastatic disease in a substantial proportion of our experiments.”

**Molecular imaging:** With that useful antigen, PSMA, as a target, the scientists are working with neuroradiologist Martin Pomper, M.D., Ph.D., (himself a previous recipient of a Walsh Fund award). “We are developing an optical agent that can be given intravenously the day before radical prostatectomy, and then imaged in real time during robotic prostatectomy,” says Lupold. “This may enable robotic surgeons to actually see the cancer at the edge of the resection during an operation, minimizing the likelihood of leaving any cancer behind.”

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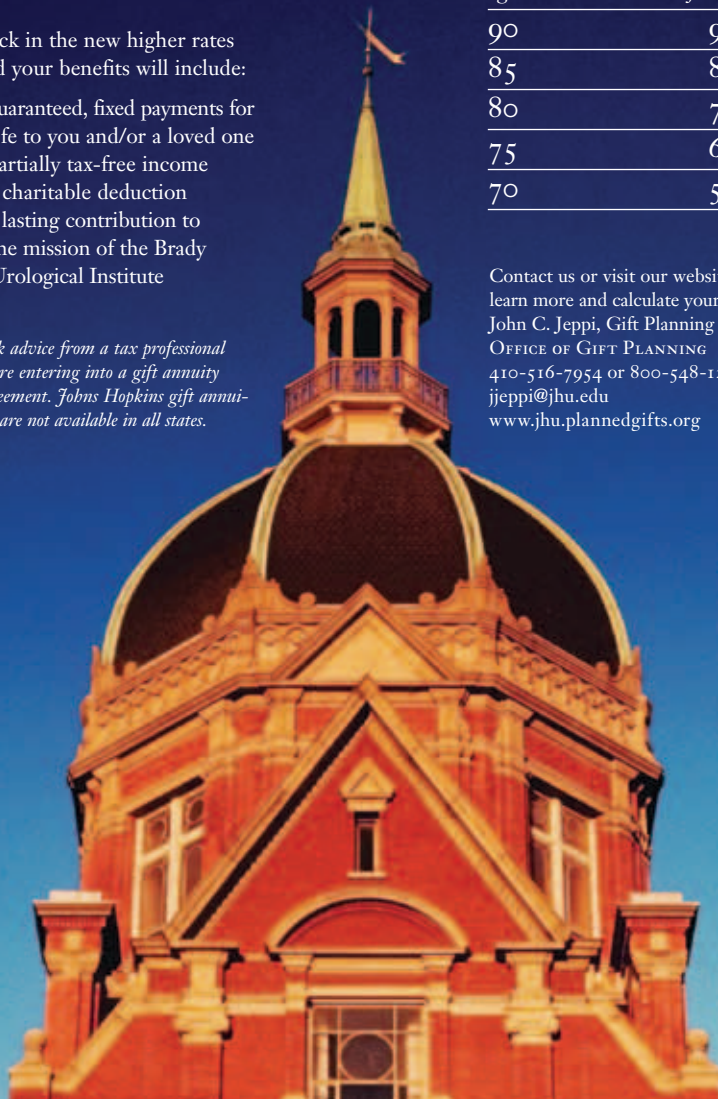
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