

# DISCOVERY

The Brady Urological Institute • Johns Hopkins Medicine

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*Don Coffey's approach to teaching is simple. Take the smartest people you can find, give them the opportunity, encouragement, and environment they need to do what they want to do, and let them get on with it.*

## Teacher's Teacher, Scientist's Scientist

This makes perfect sense, if you know Don Coffey: As a young man, when he got the overwhelming feeling that he was meant to do cancer research — although nothing in his life so far had remotely hinted that this was to be his destiny, and he might as well have had the overwhelming hunch that he should take a walk on the moon — he didn't dwell on all the reasons why this could never happen. He just figured out a way to do it.

We could devote this whole issue to one of Hopkins' greatest scholars, thinkers, mentors, and teachers. In fact, his life story would make a pretty good movie, starring an actor with great character; maybe Tommy Lee Jones could pull it off. (The Brady website has a biography; please see <http://urology.jhu.edu/about/coffey.php>). But instead, our job here is a lot harder — to give you

a glimpse in a fairly short story of a great man, who has made Hopkins a better place for the last 50 years just by being here.

The bare bones are that Coffey, born in 1932 in Tennessee to parents who never finished high school, struggled in school. He was dyslexic, but nobody knew this until he had made it through college. He failed third grade, and took five years to get through high school, where he was a track star and avid Boy Scout; "I liked everything but school," he says. He worked full-time at a bakery, and then at a textile mill, to pay his way through college, supporting his wife, Eula (who later worked as a lab technician to support him in graduate school) and their first child; he also helped out his family during this time, as his father was seriously ill. Despite his mediocre *[continued on page 2]*

THE PATRICK C. WALSH  
PROSTATE CANCER RESEARCH FUND

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## The Brady Family



Alan Partin

**Welcome to the latest issue of *Discovery*. In many ways, it is a celebration of family — our family here at the Brady, physicians and scientists working hard together, sharing not only long hours but a common mission, to make life**

**better for men with prostate cancer and their families. You could say that we've got our very own "Brady Bunch" here, and it's a lot bigger and more diverse than the one on TV. Our cover story is on Don Coffey, a man many consider to be the "father" of prostate cancer research. I was one of his graduate students, and I can attest that everyone who** *[continued on page 2]*

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works with Don Coffey, who is mentored by him or who collaborates with him, is encouraged, nurtured and allowed to flourish, and feels part of an important, one-of-a-kind family. It is hard to imagine how many lives he has touched. We are fostering a new generation of young scientists now, and all of them will bear the stamp of Don Coffey in some way.

It is amazing and humbling, too, to think that so many of our patients become part of the Brady family. The article on Page 4 celebrates two of them, Chris Evensen and Don Clark, and notes that after men like these are successfully treated — just when you'd think they would want to forget that prostate cancer ever happened, and get back to normal life — they give back, instead. They help other men and their families by sharing experiences and wisdom, and by listening to their fears and concerns; they watch out for the next generation, by encouraging their sons and grandsons to begin screening; and they even help support our research and clinical effort financially. We talk about the "reluctant brotherhood" of men with prostate cancer. But on the other side of that dark tunnel of uncertainty, we have men like these, caring survivors, and lifetime members of our family. We need to come up with a name for these men. Maybe the "dedicated fraternity." Your suggestions are welcome.

Our Brady family includes not just urologists, but faculty in many disciplines. We are joined together in numerous collaborative projects, supported by grants, such as the Specialized Program of Research Excellence (SPORE) from the National Cancer Institute, which encompasses 25 faculty and 17 staff in seven departments (see Page 7). Projects like these allow us to cross boundaries, and instead of separating scientists, so they each work on a tiny piece of the puzzle, we can bring together their unique qualities and skills with a single focus. At the other end of the funding spectrum are smaller but equally important grants from the Patrick C. Walsh Prostate Cancer Research Fund — gifts from patients and friends to young scientists with creative new approaches to fighting prostate cancer.

If you are new to the Brady family, welcome. If you have been with us a while, welcome back. I hope you will be as excited as I am to read about the tremendous work happening here.

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

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grades, he impressed people everywhere he worked and studied with his uncanny ability to look into the heart of the most complex problems.

It surprises no one that Coffey left a good-paying job at Westinghouse because, while going to night school at Hopkins, he found out about an opening at the Brady Urological Institute — which he had never heard of — working in a lab; this put him

## We asked some of his colleagues for a few words on Don Coffey

Here's a sample of what they had to say:

**H. Ballentine Carter, M.D.:**

Some favorite Don Coffey quotes:

*"Ignorance is eating you alive, boy!"*

(Often said during heated arguments about science.)

*"Don't assume anything you can prove."*

*"You must give someone permission to insult you."*

*"You are more likely to learn something when the experiment does not turn out the way you predicted."*

*"You can learn something from everyone."*

**Shawn E. Lupold, Ph.D.:**

Don has one paradigm on which I frequently ponder. He says that, while he has never baked an apple pie, nor does he know the first thing about apple pies, he could teach you how to be one of the best apple pie makers in the world. Not *the* best, but one of the best. It is straightforward approaches such as these that allow Don to look at a complicated field and make it simple. Find out who are the best in the field, talk to them, learn what makes them the best, find your own niche in the field, and start your work. One key point is not needing to be *the* best right away, but *one* of the best. Don carefully provides the advice and confidence so that you make progress and feel that you are indeed one of the best. What's more, he's done it in a way

one step closer to his goal of studying cancer. That, after a brief time, he had so impressed faculty members, including the Brady's director, William W. Scott, M.D. Ph.D., that he was put in charge of the Brady Research Laboratories — a position he would hold for 30 years — before he even had a Ph.D.; that Scott and others helped get Coffey into graduate school at the Johns Hopkins School of Medicine; and that, unbeknownst to Coffey, Scott even paid part of his stipend out of his own pocket,

so that you've achieved, more or less, on your own and can feel proud.

**Robert Getzenberg, Ph.D.:**

He inspires. He promotes the importance of young people with new outlooks as the future of the field. He does all of this in a selfless fashion — never wanting, much less asking, for the attention to be focused on him, but with a strong interest in promoting others. It is a different model of doing science, the polar opposite of a big lab with an army of postdocs. He never has had a big lab group. His impact has come from asking the most important questions and then letting people run with their ideas, with his support behind them.

**Angelo M. De Marzo, M.D., Ph.D.:**

Don has a heart for people like no other I've met. He will always stop and take time to listen about what is going on in your life, whether it is related to science, home life, or some difficulty with an interpersonal relationship or political conundrum. Don rarely says "no" when he is asked to perform virtually anything for anyone.

Another amazing thing about Don is that not only does he have this deep caring for other people, but he has an unbelievable gift of insight and the ability to perceive critical issues about a problem and then communicate highly innovative and effective solutions — almost always without directly telling his advisee what to do. The odds that one person would simultaneously possess these two incredible characteristics, the ability to care deeply for nearly everyone he encounters, and incredible insight and brilliance into all types of problems, are so small that it is difficult to comprehend.

just to help him afford to get his doctorate in biochemistry, which he earned in 1964. That Coffey, who started at Hopkins as a technician and washer of laboratory glassware, would become a full professor in five departments (Urology, Oncology, Pathology, Pharmacology, and Molecular Sciences), that for more than a year he would run the

**His colleagues are unanimous: Of all Coffey's achievements, the most important is that he has attracted, inspired, and trained the leaders in the field.**

Cancer Center — the second-largest clinical department at Hopkins — without having an M.D.; that he would be on the Principal Professional Staff at the Johns Hopkins Applied Physics Laboratory even though he's never had a course in physics. He is the Catherine Iola and J. Smith Michael Distinguished Professor of Urology. He has a professorship named after him, too, and its first recipient is one of his former graduate students, Robert Getzenberg, who succeeded Coffey as Director of the Research Laboratories.

"It doesn't make any sense," Coffey freely admits. But in a way, it does. "You don't have to know how to work on a car to drive a car," he says. "Cooking doesn't require courses. Driving doesn't require courses. Playing a musical instrument doesn't require courses." You just have to figure out how to do it, and do it well.

"Don is a genius," says longtime friend and colleague, Patrick C. Walsh, M.D., Distinguished Service Professor of Urology. He credits Coffey's "brilliant ability to simplify" as the key factor in one of Coffey's most important discoveries, the nuclear matrix of cells, the scaffolding that provides the structure of a cell's nucleus, and helps organize its DNA. In cancer cells, Coffey discovered, the nucleus looks different. "As a non-pathologist," explains Walsh, "he was able to simplify the pathology of cancer down to one rule: The nucleus is irregular. He then set out to find what makes a nucleus round, and in the process, discovered the nuclear matrix."

## A Few of Coffey's Honors and Awards

Among many other honors and awards, Don Coffey has served as President of the American Association for Cancer Research, President of the Society for Basic Urologic Research, and has served on several major editorial boards. For 19 years, he served as a member of the National Prostatic Cancer Program of the National Cancer Institute, and as National Chairman of this board for four years. He has published more than 250 research papers. Coffey has received the Robert Edwards Award from the Tenovus Institute, both the Fuller Award and the Lifetime Achievement Award from the American Urological Association, the First Society of International Urology-Yamanouchi Research Award, that society's highest research award, and the Distinguished Service Award from the American Cancer Society. He is the recipient of two Merit Awards from the National Institutes of Health. And, despite being, as he puts it, a "raving liberal," he was appointed by President George W. Bush to the National Cancer Advisory Board in 2006.

But of all of Coffey's achievements — his colleagues are unanimous on this point — the most important is that he has attracted, inspired, and trained the leaders in the field. "He is truly the father of modern science in prostate disease because of the many scientists he has personally trained, and the hundreds of others he has influenced," says Walsh. "Today, when one looks at the leaders in urological research, every one of them has the imprint of Don Coffey, one way or another." Alan W. Partin, M.D., Ph.D., Director of the Brady, didn't know he wanted to be a urologist until he spent four years working in Coffey's lab as a graduate student; before that, he had wanted to be a pediatrician. "Don Coffey has the most unique grasp of human nature I have ever witnessed," says Partin. "He has touched the lives of countless individuals both within urology and oncology, and pressed them

always to ask the question, 'if this is true, what does it mean?'"

Coffey's approach to teaching is simple. "Tell me the smartest people, and I don't care what they do, I'm helping them." A partial list of his former graduate students includes some of the top scientists in urology and oncology: Partin, Getzenberg, William Nelson, Drew Pardoll, Arthur Burnett, Bert Vogelstein, John Isaacs, Herb Lepor, Angelo De Marzo, Shawn Lupold, and William Isaacs. "All these great people," says Coffey. "It's not that I teach them anything. It's that, if you're the best, I'll give you an opportunity to do your thing, and we're on our way."

Coffey is working on the TEMT project (Temperature Enhanced Metastatic Therapy), seeking to understand why heating cancer cells makes them more susceptible to all forms of therapy. Because he is Don Coffey, his research includes how heat affects *life* — how when a hen sits on an egg, it hatches. He is 76 years old, and still going strong. "In fact, he is moving faster than ever," says Getzenberg. "Almost daily, I receive calls from him at 6 or 7 a.m., where he has been up for a while and in reading has come up with some exciting novel concepts that we should follow up on. He dedicates every day of his life to making an impact on prostate cancer, and to his family. In many ways, those of us that he has touched so deeply are part of his family. I believe that through his thinking and guidance we are getting closer to affecting prostate cancer in a significant fashion within the next several years."

Says Coffey about his work: "I've dedicated my life, I hope to die doing this. I don't need any more honors, I'm paid more than I'm worth, I probably should get out of the way, but I still have questions."

**Coffey is working on the TEMT project, seeking to understand why heating cancer cells makes them more susceptible to all forms of therapy. Because he is Don Coffey, his research includes how heat affects *life* — how when a hen sits on an egg, it hatches.**

## GIVING BACK:

## Survivors Become Part of the Brady Mission



Chris Evensen

Two men, living on two different coasts, total strangers who may never meet. And yet, they are linked forever. Not just as members of that “reluctant brotherhood” of men who have had prostate cancer, but as prostate cancer

survivors who have become part of the mission here at the Brady.

Something remarkable happens here, something hard to put into words, to many of the men who walk through our doors. Their journey starts with the diagnosis nobody ever wants to hear: “You’ve got prostate cancer.” Many of them get this unwelcome news in another city, a distant state, even another country. They

**Many of these men find Hopkins — and Hopkins finds them — at a point of soul-searching, when everything suddenly shifts into sharp focus, when life and loved ones are suddenly more precious than they ever realized, when they have many more years of living to do, and they don’t want to lose a single minute.**

start looking around, exploring, reading everything they can find, trying to figure out the best course of treatment, looking for the best doctor, and the right hospital. Many of these men find Hopkins — and Hopkins finds them — at a point of soul-searching, when everything suddenly shifts into sharp

focus, when life and loved ones are suddenly more precious than they ever realized, when they have many more years of living to do, and they don’t want to lose a single minute. They come to Hopkins, and fortunately, the vast majority are cured of their cancer.

Now, here’s an amazing thing: Just when you’d think these men would want to run screaming from the world of prostate cancer, never to have to think about it again, to get back to normal life and pretend this brush with disease and uncertainty never happened — instead, they get involved. They donate their tissue and blood samples to the Brady’s vast storehouse for further research. They help other men and their families — by listening, offering advice, a shoulder to cry on, words of encouragement, prayers. Many of them help financially, too, supporting the scientists and clinicians at the Brady who are working to cure this disease, and to make life better for the men who have it.

Two of these men are Don Clark and Chris Evensen. Don lives in New Jersey, Chris in California. Don and his wife, Becky, were planning to move across the country in February, 2009, when he was diagnosed with prostate cancer. Then began what he calls his “due diligence,” his quest for what to do next. “My first step was to search out the very best surgeon I could find in the field. I discovered that the best was Patrick Walsh.” The sale of their house fell through, and Don and Becky took a week on a lake with their two Siberian Huskies to reflect and pray about this “whirlwind of issues. It became clear what the decision was, and that it was meant to be that we were not to move and that God had opened the door to the best surgeon and the best hospital in the country.”

Chris Evensen had lived for years with the acute knowledge of prostate cancer that only comes from seeing someone die of it. His father died of the disease in 1984, and his father’s father had died either of prostate or kidney cancer. Worried that he might have inherited the risk of prostate cancer, Evensen had his PSA tested yearly; when it went up dramatically, from 1.7 to nearly 4 ng/ml, he underwent a biopsy, which was negative. Another biopsy six months later found cancer; an MRI also detected a suspicious growth on his left kidney. Evensen began talking to doctors, and decided to come to Hopkins, where Walsh would take out his prostate, and urologist Louis Kavoussi would remove his left kidney. He had both operations during the same

**Just when you’d think these men would want to run screaming from the world of prostate cancer, never to have to think about it again, to get back to normal life and pretend this brush with disease and uncertainty never happened — instead, they get involved.**

week in March, 2004. As he recovered, still in his hospital gown and pulling his IV pole with him, he wandered around the Brady, out of the hospital floors and into the research areas, where he ran into Walsh, he recalls. “We started talking about the research being done at Hopkins.” Evensen made contributions to the Patrick C. Walsh Prostate Cancer Research Fund, to Don Coffey’s professorship, and has established the R. Christian B. Evensen Professorship, which will support work in both prostate and kidney cancers. “I saw it as my way that I could help further the effort.” Still, he wanted to do more. He got involved with Michael Milken, a prostate cancer survivor who started the Prostate Cancer Foundation, and joined that group’s Board. In 2006, he joined the Board of Trustees for Johns Hopkins Medicine; he also serves as Chairman of the Johns Hopkins Prostate Cancer Advisory Board, and a member of the scientific advisory Board for the Patrick C. Walsh Prostate Cancer Fund.

In addition to his longstanding relationship with Walsh, Evensen now works closely with the Brady’s Director, Alan W. Partin, M.D., Ph.D., with whom he actively manages the Prostate Cancer Advisory Board, and works to promote the Brady Institute Internationally. He also helped develop a project plan for work on Temperature Enhanced Metastatic Therapy (TEMT), working with Hopkins scientists Robert Getzenberg and Don Coffey, in partnership with the Prostate Cancer Foundation and Safeway. Evensen and his

**“We all have the ability to make a difference here.”**

wife, Felicia, have even hosted dinners for Brady faculty members.

"We all have the ability to make a difference here," he says. With prostate cancer, "there is an awesome opportunity to at least get this disease into a chronic state. I'm not sure there will be a cure in the next five to 10 years, but we can get it to a point where it kills much fewer men than it does today." Evensen and his wife have three sons, his brother has two sons, and his sister has a son. "We're trying to educate all of them," he says, "and I intend to support the Prostate Cancer Team, as we identify and implement technologies to stop or slow down prostate cancer, so that my sons or grandsons will not face the same challenges that I did."

Both Evensen and Clark have become advocates for men with prostate cancer, in addition to supporting the work here at Hopkins. "I try to be a resource," says Evensen, "try to remove the fear of prostate cancer. I think for most men, it's a scary process. Having been through it, I try my best to help them through."

#### MAKING SENSE WHEN STUDIES COLLIDE:

## Does PSA Testing Save Lives? Two Studies, Two Different Answers. Which is Right?

Two recent studies on PSA testing — both long-awaited, both published in the March 2009 issue of the *New England Journal of Medicine* — seem to contradict each other. One of them said that screening with PSA reduced deaths from prostate cancer by up to 27 percent. The other said that PSA testing didn't work. When studies collide, how do you find the truth?

"Like many things, the devil is in the details," explains Patrick C. Walsh, M.D., Distinguished Service Professor of Urology. But in this case, he adds, "understanding these details could save your life."

The European study, a landmark project carried out in seven countries, looked at

## The Bottom Line: Testing Does Save Lives

**The European study:** 162,000 men, one group randomly assigned to PSA screening every four years; men in the other group not screened. The men were followed for as long as 14 years. Results: A 27-percent decrease in prostate cancer deaths.

**The U.S. study:** Half as large as the European study. At seven years, a time point too early to be of value, showed no improvement in deaths from prostate cancer. Because 50 percent of the men in the control group actually underwent PSA testing, this study did not test "screening versus no screening," but "more screening versus a little less." Also, fewer than one-third of the screened men with an elevated PSA actually underwent a biopsy.

162,000 men. One group of these men was randomly assigned to PSA screening every four years; men in the other group were not screened. These men were followed for a long time, some as long as 14 years. Of the men who were screened, there was a 27-percent decrease in prostate cancer deaths.

"This is similar to the 30-percent reduction in deaths from breast cancer in women who undergo mammography, and the 33-percent drop in deaths from prostate cancer that occurred in the United States between 1994 and 2003 following the introduction of PSA screening," says Walsh. "The results from the European study unequivocally demonstrate that PSA testing can save lives."

What happened in the second trial? The American study was only half as large as the European one, and it had many major flaws, says Walsh: It compared screening with PSA every year for six years with no screening afterward, versus no screening at all, and at seven years, it showed no improvement in deaths from prostate cancer. The biggest problem here, explains Walsh, is that in terms of statistics, "death from prostate cancer at seven years is meaningless. Screening and aggressive treatment, first of all, are meant for men with at least a 10-year



PSA testing pioneers, from left, Bill Catalona and Fritz Schroeder. Schroeder, who led the European Randomized Study on Screening for Prostate Cancer, credits Catalona for galvanizing his interest in this project. "In 1990, when Dr. Catalona was our visiting professor at Erasmus University in Rotterdam, I saw the data that he would soon publish in the *New England Journal of Medicine*, which showed that PSA testing led to the earlier diagnosis of curable disease. This inspired me to initiate pilot studies," which culminated in this landmark study.

life expectancy. Any man who dies within seven years of being diagnosed with prostate cancer has advanced, non-curable disease at the time of diagnosis, and would not benefit from PSA screening." In the European trial, there was no improvement in survival at seven years, either. It was just too soon.

**"If the authors had set out to design a study to discredit PSA testing, it would have been difficult to do a better job."**

The U.S. trial failed to achieve some important milestones that have been shown in successful screening trials. For example, screening for breast cancer has led to an increase in the

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**“If you’re not worried about dying from prostate cancer, do not undergo PSA testing. On the other hand, if you are a healthy man aged 55 to 69 who does not want to die from prostate cancer, the European trial provides conclusive evidence that PSA testing can save your life.”**

number of cases diagnosed, and a decrease in the number who are found too late to be curable. The European prostate cancer trial showed a 71-percent increase in the number of new cases, and a 41-percent decrease in the number of men diagnosed with incurable disease. “It just makes sense that the longer these men are followed, the greater decrease we can expect to see in prostate cancer deaths,” says Walsh. In contrast, the U.S. study found only a 17-percent increase in the number of new cases, and no decrease in the number of men diagnosed with advanced disease. Because of the study’s design, even if men are followed longer, “unfortunately the results will not change,” says Walsh.

What’s wrong with this study? First, Walsh says, is that “it did not test screening versus no screening. It just compared more screening versus a little less screening.” Second, fewer than one-third of the men in the U.S. trial who developed a PSA greater than 4 actually underwent a biopsy. Walsh finds this aspect of the study most difficult to understand. “If most of the men with elevated PSA levels never underwent a biopsy, how can anyone expect this trial to show that screening saves lives? And finally, the American study used an outdated cut-off point for PSA — greater than 4.0, as opposed to greater than 3.0 in the European study — as the trigger-point for a biopsy. “If the authors had set out to design a study to discredit PSA testing, it would have been difficult to do a better job,” he says. It could be that the U.S. investigators were trying to simulate what would happen if every man in the United States had a PSA performed, but

few followed up with a biopsy or treatment. “If that were the question, I think we could have already guessed at the answer without spending \$110 million.”

For prostate cancer screening, Walsh adds, “10 years is the earliest time at which we would expect to see any benefit. For a 50-year old man who is going to be alive for another 35 years, those odds are entirely different, and screening is very worthwhile.” The key to successful screening is knowing who is most likely to benefit from it, “to avoid over-diagnosis in men who are too old or too ill to live longer than 10 years, and to avoid over-treatment in men over age 65 who have low-volume disease. Most of all, it is imperative for us as physicians to continue to improve the quality of treatment. If one day we could reduce the side effects to a minimum, the debate would end.

The “take-home message” here is simple, Walsh believes. “If you are the kind of person who doesn’t wear a seat belt or go regularly to the dentist or your family doctor for a check-up, and you’re not worried about dying from prostate cancer, do not undergo PSA testing. On the other hand, if you are a healthy man aged 55 to 69 who does not want to die from prostate cancer, the European trial provides conclusive evidence that PSA testing can save your life.”

#### IN ADVANCING PROSTATE CANCER:

## Genetic Cutting and Splicing Disaster



William G. Nelson

says oncologist William G. Nelson, M.D., Ph.D., “gene defects that give it the ability to grow uncontrollably, to spread to the bones and other organs, and to threaten life.”

Picture a snowball tumbling down a hill. It doesn’t just get bigger, it gets more complicated, picking up a rocks, twigs, and other little bits of debris. Something similar happens with cancer. As it advances, it acquires things, too,

One of these genetic events is an unfortunate switching of places of DNA on a chromosome — like a LEGO, taken off of one brick and stuck back on another. This particular brick, a gene with the alphabet-laden name of TMPRSS2, is normally regulated by male hormones, or androgens. But in prostate cancer, it breaks away from its normal site and joins another gene, called ERG, which encourages cancer cells to grow.

The unwelcome result of this fusion between TMPRSS2 and ERG is that “prostate cancer cells respond to androgens by exhibiting rapid growth,” says Nelson, the Director of the Sidney Kimmel Comprehensive Cancer Center. In recent work with scientists Vasan Yegnasubramanian and Michael Haffner, Nelson learned more about how this happens. Androgens use an “untangling enzyme,” which normally breaks and reconnects DNA with no ill effect, to do the job. Nelson compares how it works to what happens when a cassette tape breaks, and all of the tape spills out in a messy snarl. “One way to untangle the tape is to cut and rejoin the tape segments,” he says. “If a segment is cut but not accurately rejoined, then an intact cassette tape can be generated by splicing the end somewhere else, leading to a rearrangement of the recorded material on the tape.”

**“This DNA mess is like what happens when a cassette breaks, and the tape gets all tangled up.”**

Similarly, the untangling enzyme cuts and splices. In cancer, the enzyme accomplishes the first part of its job — breaking segments of DNA — just fine. However, it doesn’t hook them back up, “leaving free DNA ends to plug in haphazardly to other sites in the genome,” Nelson says. “This mechanism enables the male hormone, testosterone, to cause genetic damage in prostate cells.”

#### MAKING A GIFT

If you are interested in making a gift to support The Brady Urological Institute, or if you are considering a gift of stock, real estate, IRA, or other asset, please call the Development Office at (410) 516-6160.

## SPORE:

## Grants Support Collaboration, Translational Work

When the National Cancer Institute (NCI) awards a SPORE grant (Specialized Program of Research Excellence), it tells a medical center, in essence, “We like the way your doctors and scientists are working together. We like the way you have people from different disciplines and maybe even different

**A SPORE grant means, “We like the way your doctors and scientists are working together, tackling a common goal.”**

institutions tackling a common goal.” The aim of a SPORE grant is “translational” research: Moving a novel idea — one that has the potential to improve detection, diagnosis and treatment of cancer, prevent cancer-caused deaths, prolong survival, and improve quality of life — from a scientist’s brain to the laboratory to, eventually, patients in clinical trials.

As you may imagine, the NCI doesn’t award too many SPORE grants; there are fewer than a dozen focused on prostate cancer. Hopkins recently had its SPORE grant renewed, with an excellent score. Better yet, says William G. Nelson, M.D., Ph.D., Director of the Sidney Kimmel Cancer Center, “in comparison with other Prostate Cancer SPOREs across the country, we have such a rich pipeline of discoveries headed toward the clinic that all of the projects described in the application were new since the previous submission five years ago. Even more impressively, each of our previously funded SPORE projects had reached its translational research milestone, moving on to later stage development supported by other types of funding.”

Nelson recently co-chaired a 60-member Translational Research Working Group, charged by the NCI with coming up with strategies to streamline the journey from concept to laboratory to the patient’s bedside. One of their results was a set of devel-

## Interested in Participating in a Clinical Trial?

One of the advantages of receiving care at a major academic medical center is that this is where the latest innovations are being studied. There are always clinical trials underway at Hopkins, for men at every stage of prostate cancer. This includes men getting ready for primary therapy (surgery or radiation treatment); men with a rising PSA after treatment; men with metastatic cancer, and men with metastatic disease who have already undergone chemotherapy.

If you are interested, please see this page on the Brady website: <http://urology.jhu.edu/research/trials.php>, and talk to your doctor. Before you enroll, Brady staff and faculty will make sure that you know how it works; whether there are any potential side effects; and that you know that you are free to stop being in the study whenever you want.

Participating in a study often means more than the opportunity to get an early chance at a new breakthrough. Many who volunteer to take part in a medical study do it because they feel they are helping a greater cause — that their participation will advance medical science and, ultimately, help other people. You can also find clinical trials by going to this website, run by the Sidney Kimmel Cancer Center at Hopkins: <http://www.hopkinskimmelcancercenter.org/index.cfm/cID/37>

opmental pathways to prioritize, monitor, and manage translational research efforts at SPORE centers. “These pathways place a premium on newly discovered molecular targets for diagnostic and drug development,” says Nelson. “For prostate cancer researchers at Johns Hopkins, whether supported by the SPORE Program, the Patrick C. Walsh Prostate Cancer Research Fund, or other sources, this focus is great news because this is one of our great strengths. Our research teams are the best in the world at bringing both a savvy for the behavior of prostate cancer as a disease and a deep knowledge of

the molecular mechanisms that drive prostate cancer development and progression.”

Four Brady scientists — Mohamad E. Allaf, M.D., Tamara Lotan, M.D., Jun Luo, Ph.D., and Prakash Kulkarni, Ph.D. — recently received funding as part of this SPORE program. Here’s a brief look at some of their work:

### The Next Best Thing to the Surgeon’s Fingertips: Ultrasound Elastography

Over the last few years, robot-assisted laparoscopic radical prostatectomy has emerged as an exciting, minimally invasive alternative to the traditional open radical prostatectomy. There’s just one drawback. “During open surgery, which remains the gold standard today, surgeons use tactile feedback to determine whether cancer extends outside of the prostate” says Mohamad E. Allaf, M.D., Director of Minimally Invasive and Robotic Surgery. If the surgeon feels anything suspicious, this could lead to removal of more tissue. “Robotic surgery does not offer this tactile feedback, and this has raised concerns regarding the surgeon’s ability to appreciate differences in tissue texture or firmness along the prostate surface.” The landscape immediately surrounding the prostate is treacherous for surgeons; for example, it is easy to cut or damage the tiny, delicate nerves on either side of the prostate that are responsible for erection (these are known as the neurovascular bundles of Walsh). “This sometimes means a dilemma for the surgeon,” says Allaf. “Remove too much tissue needlessly and the patient loses erectile function. Remove too little, and risk leaving

**Translational research is moving a novel idea from a scientist’s brain to the laboratory to, eventually, patients in clinical trials.**

cancer behind.” To address this, Allaf, along with Emad Bector, Ph.D., an engineer in the division of Medical Imaging Physics, is working on a new means of imaging called elastography imaging. An advanced form of ultrasound, this technology helps the surgeon know where tissue is harder or more dense. “Elastography imaging is noninvasive, relatively inexpensive, and does not expose the patient to

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radiation,” says Allaf. Better yet, it has “the potential to provide the surgeon with real-time information regarding the course of the neurovascular bundles. We know that there is variability in the location of these critical nerves, but to date there is no reliable way to image them during the operation.”

Their preliminary work, on resected prostate specimens, has been encouraging. “We were able to consistently identify cancerous and benign lesions,” says Allaf. Next, in animal studies, they were able to image the neurovascular bundles, as well. Now, they are working on integrating this technology into a robotic arm. “We hope that our work will provide surgeons with the best of both worlds,” he adds, “the latest in technology and the irreplaceable ‘human touch.’”

#### **Tubes and Prostate Cancer: Why Shape Matters**

One telltale feature of prostate cancer that makes it easy for pathologists to spot under the microscope is that it makes tubes — simple little tubes of cells, which poke between normal prostate cells. As far as prostate cancer pathology goes, tubes are good. The vast majority of these tube-shaped cancers are confined to the prostate at radical prostatectomy, “and patient survival is generally excellent,” says pathologist Tamara Lotan, M.D. But as the cancer cells advance, they lose this tube-making ability, and begin to grow in more complicated structures. “Then, the Gleason grade increases, and patients are more likely to develop recurrences, and possibly distant metastases.”

Nobody knows why shape matters so much in prostate cancer, and why, when tumor cells stop growing in tubes, the cancer becomes more aggressive. Lotan and colleagues are working to answer these questions. Outside of cancer, she notes, the only other time that prostate cells grow in tubes is before birth, during embryonic development. “By first understanding the signaling pathways and proteins that drive normal prostate cells to grow as tubes, we will have a better idea of how disturbances in these pathways might lead to the inability of cancer cells to form these structures.” The embryonic mouse is a perfect laboratory model for investigating how, very early on, normal prostate cells make these tubes and then, as part of normal life, stop making them, Lotan adds. “Using cutting-edge

microscopic techniques, we can literally watch the embryonic mouse prostate tissue form tubes over two to four days, and watch what happens to the tubes when we alter specific proteins.”

Lotan and colleagues are particularly interested in the role of a gene that is usually lost in prostate cancer cells, a tumor suppressor called PTEN. “PTEN is known to play an important role in the movement of immune cells and in tube formation in kidney cells,” Lotan explains. “Also, it is most commonly lost in high Gleason-grade tumors — the very same tumors that fail to form tubes in human patients and are more likely to be associated with a poor clinical outcome.” After the scientists have figured out the normal role of PTEN in prostate cells, they will study the effect of its loss in prostate cancer cells, to see how this affects the cancer’s ability to spread.

#### **New Clues May Help Predict Who Will Benefit Most from Hormonal Therapy**

Hormones are chemical signals, and they are picked up by specific proteins, called receptors — think of a baseball and a catcher’s mitt. Male hormones, such as testosterone, are called androgens, and their designated “catcher’s mitts” are called androgen receptors. But these receptors don’t just catch the ball; instead, when they make contact with an androgen, they spring into action, issuing commands to cells to produce genes that, in turn, help the body’s cells grow and function. This is known as the “androgenic signaling pathway,” and since 1941, doctors have used it as a gateway to treat men with advanced prostate cancer.

Hormonal therapy means taking away the male hormones that nourish the prostate; it can also mean blocking the androgen receptor, to keep out the hormones’ messages. For some men, hormonal therapy can keep cancer at bay for many years, but it comes at a steep price that includes loss of libido, personality changes, a higher risk of heart problems, osteoporosis, anemia, and a decline in cognitive function, among other side effects. It also doesn’t work the same way in every man; some men receive the cancer-stalling benefits for only a few months.

“Because the clinical benefit is limited in time, and the side effects are additive with longer treatments,” says scientist Jun Luo, Ph.D., “there is a pressing need to develop new tools to help determine whether and when to initiate hormone therapy.”

Luo and colleagues believe they may have some good new tools in the making: They have discovered seven new androgen receptors that work differently from the “normal” androgen receptor, Luo explains. “One key feature of these variant androgen receptors is that they can activate the androgenic signaling pathway — even without andro-

#### **Which men will have the best luck with hormonal therapy?**

gens.” In work recently published in *Cancer Research*, Luo and colleagues found elevated levels of these variant androgen receptors in men who failed hormonal therapy. They also found higher levels in men who had not received hormone therapy, but had more advanced prostate cancer.

This work suggests that these new receptors may affect how well — or poorly — a man will do on hormonal therapy. Luo and colleagues are working to develop a test using these findings to help predict which men will have the best luck with hormonal therapy, and which men could be saved the side effects of a treatment that will not be of great long-term help.

#### **Is It Aggressive Cancer? On the Trail of New Biomarkers to Help Find Out**

What kind of prostate cancer is it? Everybody wants to know — men with prostate cancer, the doctors treating them, and scientists like Prakash Kulkarni, Ph.D., who are working to develop new molecular tests to answer this question. Is the cancer aggressive? If so, it needs to be treated right away. But if it’s not, if it’s lazy, slow-growing, not particularly ambitious, and poses no im-

#### **New biomarkers may be able to predict aggressive cancer that has already metastasized.**

mediate threat, then a man can afford to delay treatment — sometimes, indefinitely.

Kulkarni is working with a group of proteins called Cancer/Testis Antigens (CTAs), and he believes he may be on the trail of new biomarkers for prostate cancer — especially for aggressive cancer, and even cancer that has already metastasized. Growing evidence,

he says, suggests that these CTAs are linked to stem cells, and that in normal adult tissue, they're turned off. "However, genetic changes in cancer can cause them to reactivate," and the result is bad news — a more malignant cancer. "In addition to their role as cancer-specific antigens, several CTAs have also shown considerable promise in predicting the course of other malignancies, including neuroblastoma, gastrointestinal tumors, multiple myeloma and cervical carcinoma." Also, if several CTAs are active at once, this has been shown to make several kinds of cancer more resistant to treatment. "Using a variety of molecular biology, cell biology and immunochemical techniques, we hope to identify CTAs, and to develop novel biomarkers that may aid in accurate diagnosis, prognosis, and predicting response to therapy in men with prostate cancer."

## How Your Genes Affect PSA

For years, urologist H. Ballentine Carter, M.D., has been studying PSA, looking for ways to make it a more accurate crystal ball. Among his many breakthroughs are the concept of PSA velocity — looking for changes in a man's PSA levels over time — and the development of guidelines for when and how often men should be tested for prostate cancer. Carter has spent much of his career poring over the records of men in the Baltimore Longitudinal Study of Aging (BLSA) a huge treasure trove that includes, among other data, blood samples taken over decades from men — many of whom eventually developed prostate cancer. Carter has identified changes over time in those men as they headed toward cancer.

In a recent study, published in the *Journal of Urology*, Carter and urology resident Stacy Loeb, M.D., together with colleagues at the BLSA, asked a different question, based on work led by Hopkins scientists showing links between certain genetic variations and a man's risk of prostate cancer. Some of these genetic variations are located near the PSA gene, and are also associated with the PSA level. Would it be possible, Carter and Loeb wondered, to use these genetic tests — which help identify men at higher risk of

**Men with specific genetic landmarks had a 28-percent higher risk of developing prostate cancer for every one-unit rise in PSA — say, from 2.5 to 3.5. But for men without these suspicious genes, using this equation, prostate cancer risk was lower.**

developing prostate cancer — to help interpret the PSA level?

Carter and Loeb studied 505 men from the BLSA; 61 of these men were diagnosed with prostate cancer. They found that for each one-unit increase in PSA — from 2.5 to 3.5 ng/ml, for example — the men's risk of developing prostate cancer increased by 18 percent.

Then they plugged in the genetic data, and "the equation changed considerably," says Loeb. Men with specific genetic landmarks — or particular variations, identified at chromosomes 10 and 19 — had a 28-percent higher risk of developing prostate cancer for every one-unit rise in PSA. Interestingly, while the men with the suspicious genes had a much higher-than-average risk using this genetic equation, prostate cancer risk was correspondingly lower for men without this genetic profile. "Men who did not have these genetic variants had only a 10-percent increase in risk for each one-unit increase in PSA," says Loeb, who also notes that the relationship between these variants and prostate cancer risk depends on the PSA level.

Overall, these results suggest a couple of things, adds Carter. One is that "genetics seem to influence a man's risk of having prostate cancer at a given PSA level." Another is that one day, future prostate cancer screening might include a man's genetic profile along with the PSA measurement, "giving him a custom-tailored PSA result, and providing an even more accurate assessment of his risk for cancer."

## With Focal Therapy, Some Prostate Cancer May Be Left Behind

Do you have friends who are considering focal cryotherapy — or even paying \$25,000 in cash to go to the Dominican Republic for HIFU (High Intensity Focal Ultrasound)?

Jonathan Epstein, M.D., the Reinhard Professor of Urologic Pathology, has been concerned about a new trend in treatment designed to minimize side effects by just removing the part of the prostate that has cancer. It's called focal therapy, and it's based on the assumption that the biopsy is infallible.

**Think of dandelion seeds on a windy day, and imagine that your job is to catch and account for each one. Each core from a needle biopsy shows only one-thousandth of the prostate. So even if a biopsy shows that cancer is just found on one side of the prostate, that might not be the case at all.**

One reason prostate cancer can become such a formidable enemy is that it's like dandelions in the field, sprouting up in multiple area of the prostate all at once. Even worse, think of dandelion seeds on a windy day, and imagine that your job is to catch and account for each one. Each core from a needle biopsy shows only one-thousandth of the prostate. This means that even if a biopsy shows that cancer is just found on one side of the prostate, that might not be the case at all. A needle biopsy has been compared to looking *with* a needle in a haystack, because it takes such tiny cores of tissue. Even if it takes a lot of them — more than a dozen — that doesn't mean that cancer is *not* in the remaining tissue. And it doesn't mean that this cancer can't be significant.

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“Definitive therapy for prostate cancer, whether by surgery or radiation therapy, intends to treat the entire prostate,” says Epstein. “The greatest concern with focal therapy is that it will leave significant cancer behind on the side not treated.” Until now, no one had ever tried to answer this question. In work recently published in the *Journal of Urology*, Epstein and colleagues investigated 100 consecutive radical prostatectomy specimens in which the needle biopsy showed that cancer was restricted to one side of the prostate. When they looked at the entire gland, would the other side turn out to be cancer-free? Would it have been safe to leave this prostate tissue behind?

“Each prostate had, on average, about three separate tumors,” says Epstein, and in general, most of the tumor on the opposite side from the positive biopsy site was very small. But one out of five men turned out to have potentially significant cancer — cancer that was larger, of higher grade, or cancer that had even extended out of the prostate — on the other side of the prostate. “Had these men undergone focal therapy, this would not have been treated.” An unanswered question, he adds, is, “how many more men who had small tumors on the side opposite to the biopsy may have progressed with adverse outcomes over time, if they had selected focal therapy? Patients should be told the risks of leaving cancer behind before undergoing this experimental therapy.”

#### FOR MEN CHOOSING ACTIVE SURVEILLANCE:

## PSA Tests Are Not Enough; You Need a Biopsy, Too

In less than two decades, regular screening for prostate cancer has already saved thousands of lives; men are being diagnosed with cancer an average of five to 10 years earlier than they used to be, and the vast majority are diagnosed with curable disease. Could there possibly be a downside to such wonderful news?

Actually, there could. Scientists have long known that some men who get prostate cancer get the very “best” kind — if there is such



Ross, Loeb, and Carter: Changes in PSA alone make an inadequate “trigger for intervention.”

a thing — imaginable. It is slow-growing, mild-mannered, and it just kind of treads water, bobbing around for years in the prostate, never spreading, never causing a problem. These men used to be diagnosed with prostate cancer only at autopsy. They lived their whole lives and died of something else, and never even knew they had cancer.

Today, some men diagnosed with very early, low-risk prostate cancer are choosing active surveillance instead of immediate treatment, hoping that their cancer, too, will be the “do-nothing” kind. This is not the same as “no treatment,” and it’s not passive, like the old “watchful waiting,” which meant waiting to take action until symptoms developed — and which, unfortunately, often meant waiting until the cancer was not curable. Instead, active surveillance involves close monitoring, with repeated PSA tests, digital rectal examinations, and yearly prostate biopsies. If there is any sign that the disease has progressed, the men receive curative treatment — surgery or radiation therapy — right away.

**In some men, the cancer progressed, but their PSA hardly changed at all.**

In many practices, these men are followed simply by measuring their PSA levels; if the PSA begins to go up, the doctor recommends a biopsy. At Hopkins, we’ve believed for many years that PSA alone is not an accurate guide. For this reason, the guidelines established by H. Ballentine Carter, M.D. have always included yearly biopsies — whether or not the PSA goes up. Recently, Hopkins residents Ashley Ross, M.D., Ph.D., and Stacy Loeb, M.D., asked what would have happened if we had just used changes in PSA alone to serve as the “trigger for intervention.” In other words, says Carter, “do men really need to undergo the yearly biopsies?” The answer turns out to be yes.

Ross and Loeb studied 290 men from the Johns Hopkins Active Surveillance Program, which Carter, professor of urology and oncology, and Jonathan Epstein, M.D., the Reinhard Professor of Urologic Pathology, started in 1994. They found that PSA levels tended to change at a slightly higher rate, or velocity, in men with progression of disease, compared to men whose cancer did not progress. However, notes Ross, “some men with progression had very little change in their PSA over time, and some men without progression had large changes in PSA over time.”

Thus, changes in PSA alone “were not reliable enough,” says Carter, “when a man’s life

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

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

For four years, The Patrick C. Walsh Prostate Cancer Research Fund has put out the welcome mat, inviting all scientists at Johns Hopkins, in all disciplines, to compete for a grant. The only requirement is that they think have a good idea that could help us understand prostate cancer better. This Fund, blessed by the tremendous generosity of our patients and friends, has raised \$30 million. In an era of economic uncertainty and governmental budget woes — despite the increasing number of men diagnosed each year with prostate cancer — this generosity is truly remarkable. Never has this support been more vital.

We are now able to provide \$1 million a year to fund proposals from the best and brightest Hopkins scientists in many departments, including Oncology, Radiation Oncology, Cell Biology and Anatomy, Pathology, Pharmacology, Epidemiology, and Urology. This year, we received applications from 25 Hopkins scientists, as well as requests for continued funding from last year's awardees. The applications were reviewed by a scientific advisory board composed of distinguished Hopkins scientists and two lay members, R. Chris Evensen and Samuel Himmelrich. This year, we awarded more than \$1 million to 13 recipients with new ideas. Some of their work is described below.

## THE 2007–2008 AWARDEES

**Charles Drake**, M.D., Ph.D.

*Department of Oncology*

**William B. Isaacs**, Ph.D.

*Irene and Bernard L. Schwartz Scholar  
Departments of Urology and Oncology*

**Marikki K. Laiho**, M.D., Ph.D.

*Division of Molecular Radiation Sciences  
Department of Radiation Oncology*

**William G. Nelson**, M.D., Ph.D.

*Nancy and Jim O'Neal Scholar  
Department of Oncology*

**Edward M. Schaeffer**, M.D., Ph.D.

*Virginia and Warren Schwerin Scholar  
Department of Urology*

**Bruce J. Trock**, Ph.D.

*Carolyn and Bill Stutt Scholar  
Department of Urology*

**Srinivasan Yegnasubramanian**, M.D., Ph.D.

*Dr. and Mrs. Peter S. Bing Scholar  
Department of Oncology*

**Hui Zhang**, Ph.D.

*Department of Pathology*

us as adults, too, in places like our hair, skin, bone marrow, intestine, and prostate. Not as versatile as the embryonic form, they can only make a limited number of cell types.

"Normally, cells can divide only a few times," explains De Marzo, "before they per-

### Why are stem cells so interesting to scientists who study cancer?

manently exit from the cell cycle. They either die, or they undergo a process called "differentiation," in which they mature through a number of steps, ultimately becoming fossilized, non-dividing versions of their former selves." Stem cells, on the other hand, can divide indefinitely. In this, they are like cancer cells. But are the tissue stem cells the actual cells that go on to become cancer cells? This is a popular idea in science at the moment. Or, do other tissue cells somehow revert back to an embryonic, stem-like state?

De Marzo tends to think it's this second scenario. One of the abnormal things in a cancer cell is a structure called a nucleolus. "It's a little factory," he says, "that produces crucial components, including ribosomes; cancer cells need ribosomes to reproduce efficiently." De Marzo and colleagues recently have uncovered a potential new link between stem cells, cancer cells, and the nucleolus. It's a gene called MYC (pronounced "mick"). "MYC overproduction has been implicated in driving the formation of prostate cancer and many other cancers," says De Marzo. Recently, a study led by De Marzo's laboratory found evidence that MYC can cause prostate cells to induce a set of genes that are expressed together mostly in embryonic stem cells, and not tissue stem cells. "Thus, MYC appears capable of reactivating maturing prostate cells," says De Marzo, "acting as the ultimate fountain of youth, so that they become like embryonic stem cells, and keep on renewing themselves and dividing." The study was conducted by Cheryl Koh, a graduate student in pathobiology, in collaboration with Martin Aryee, Ph.D., Vasan Yegnasubramanian, M.D., Ph.D. and Bora Gurel M.D., at the Sidney

## THE 2008–2009 AWARDEES

**Angelo M. De Marzo**, M.D., Ph.D.

*The Peter Jay Sharp Foundation Scholar  
Department of Pathology*

**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.

*Beth W. and A. Ross Meyers 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*

### Stem Cells, Prostate Cancer Cells, and Maybe, a Way to Stop Uncontrolled Growth

In the world of cells, nobody starts out as a cancer cell. Instead, a cancer cell is a normal cell that has gone bad, through a series of changes that allows it to grow and divide without stopping, and worse, to move into other regions of the body. Angelo M. De Marzo, M.D., Ph.D., the Peter Jay Sharp Foundation Scholar, describes a cancer cell as a "caricature of a normal cell."

What do stem cells have to do with this process? And why are scientists who study cancer so interested in them? There are two major types: The most controversial stem cells, embryonic stem cells, are in all of us before birth. They are the ultimate chameleons, they can become any type of cell in the body. And then there's the tissue stem cell. These aren't just in embryos, they're in all of

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

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Kimmel Comprehensive Cancer Center, and Chi Dang, M.D., Ph.D., from the Nathans Institute of Genetic Medicine at Hopkins.

One of the genes induced by MYC is called fibrillarin, which concentrates in the nucleolus, and which Koh and Gurel found is overproduced in prostate cancer cells. What implications does this have? “The really exciting part,” says De Marzo, is that when Koh turned down the production of MYC or fibrillarin, “the cancer cells lost their stem cell properties and could no longer proliferate. This raises the possibility that treatments that target the abnormal nucleolus may be a new avenue to pursue in the search for ways to prevent and treat prostate cancer.”

### A New Genetic Target for Preventing Tumor Growth



Peter Devreotes

Scientists keep breaking down the steps of cancer, into smaller and smaller parts. For example, the process of making a tumor, and then having that tumor spread, or metastasize, involves chemical signals that go awry.

One very important signal that gets muddled is a lipid molecule called PIP<sub>3</sub>. Normally, two key enzymes keep this molecule on a pretty tight leash, and this control in turn, helps keep cell growth in balance. The two enzymes are P13K, and PTEN. “P13K is a ‘go’ signal for cell growth and migration,” like the accelerator on a car, explains Walsh Scholar Peter Devreotes, Ph.D., Professor and Director of the Department of Cell Biology, “while PTEN is the corresponding ‘stop’ signal,” or the brakes. Genes like PTEN, which normally keep cells in check, are called tumor

**Imagine trying to drive a car when someone has tampered with the brakes. That’s what cell growth is like in cancer — unchecked. But what if we can fix the brakes?**

suppressors. “PTEN is one of the most frequently mutated tumor suppressors in prostate cancer,” says Devreotes. When it is disrupted, the effect is like tampering with the brakes.

PIP<sub>3</sub>, the lipid molecule, lives on the cell’s outer membrane. Although PTEN’s job is to target this molecule, only a few PTEN molecules actually make contact with it at the surface of a cell. But scientists have figured out how to tweak PTEN through genetic engineering, and dramatically increase its ability to make contact with PIP<sub>3</sub>. This doctored version of PTEN is called PTENA<sub>4</sub>, and “it’s proven to be much more effective than normal PTEN in providing a ‘stop’ signal, by reducing the amount of the lipid PIP<sub>3</sub>,” says Devreotes.

Devreotes and colleagues found that, in shape, PTEN contains a highly flexible tail, and guessed that PTEN could regulate itself by attaching, or binding, this tail to the rest of the protein. When the tail was bound, PTEN would be in a closed form; when it was released, PTEN would be in an open form. “The open form would bind more strongly to the membrane than the closed form,” he says. “To test this hypothesis, we cut off the tail, and found that the binding of the body of PTEN to the membrane was indeed very strong, like that of PTENA<sub>4</sub>.” Then the scientists found that the body and tail could bind tightly to each other.

This work suggests that controlling PTEN is critical in preventing tumor growth and formation. The next step is “to visualize the exact site where the body and tail regions of PTEN interact,” Devreotes says. “By doing so, we hope this will allow us to target these regions, in order to open and activate PTEN, and allow for the possibility of restoring normal cell growth.”

### RNA’s Roles in Advanced Prostate Cancer, and Possibly in its Treatment



Shawn Lupold

Twenty years ago, scientists considered RNA (ribonucleic acid) to be mainly a genetic middleman. DNA was the big attraction — the Oxford English Dictionary of genetics, the ultimate reference book in the human library,

says Shawn Lupold, the Phyllis and Brian L. Harvey Scholar. The transfer of information in the cell goes from DNA, which is in the cell’s nucleus, to RNA. Like a town gossip, RNA then gets very busy, taking the information to machinery that makes proteins, and then on to the newly synthesized proteins, which do the work of the cell. But RNA has other roles, too, scientists have discovered, far beyond acting as a messenger, says Lupold. His research largely focuses on RNA, how it works in prostate cancer, and its potential usefulness in diagnosing or even treating the disease.

Several years ago, scientists discovered that cells naturally copy bits of RNA, which then can turn off, or inhibit, other bits of RNA; this is known as “RNA interference,” and the RNA — so good at spreading messages — can block them, too, short-circuiting the transfer of information from DNA to protein. “In other words, this is a newly discovered off-switch for cellular pathways,” says Lupold. “Not surprisingly, cancer cells take advantage of this pathway for their own growth and survival by turning off growth inhibitory pathways.” In a new study done in Lupold’s laboratory, Judit Ribas, Ph.D., wanted to know if androgens (the same male hormones that drive the growth of prostate cancer) control these inhibitory RNAs, known as microRNAs, in prostate cancer. “We found that one microRNA, called miR-21, was directly activated by the androgen signaling pathway,” Lupold continues. “When miR-21 is expressed at higher-

than-normal levels, it turns off unknown growth-inhibitory pathways and makes prostate cancer cells and tumors grow more rapidly. Importantly, we found that just having an elevated level of miR-21 was sufficient to generate hormone-refractory prostate cancer,” advanced cancer that no longer requires androgens to grow. This work, published in September in *Cancer Research*, was funded by the Patrick C. Walsh Prostate Cancer Research Fund and the Department of Defense. Lupold and colleagues are studying miR-21 to see if it is an early marker for aggressive prostate cancers. “We’re also inter-

**Just having a higher level of miR-21 could create advanced cancer that no longer needs hormones to grow.**

ested in developing miR-21 inhibitors for the treatment of advanced prostate cancers.”

In another RNA-related project, Lupold and colleagues are investigating the use of certain RNAs as a way to make cancer cells more susceptible to radiation. Xiaohua Ni, Ph.D., a fellow in Lupold’s laboratory, is using synthetic “small interfering RNAs,” known as siRNAs, to inhibit target messenger RNAs inside the cell, using the same interference pathway favored by microRNAs. Ni is working with Theodore L. DeWeese, M.D, Chairman of Radiation Oncology and Molecular Science. “Cancer cells become highly sensitized to radiation therapy when the cells’ DNA repair machinery is inhibited,” notes Lupold. “The idea is that with these siRNAs, we can selectively inhibit DNA repair genes and allow physicians to use lower levels of radiation while achieving the same or greater therapeutic effect. If we can selectively target these siRNAs to the prostate, we can reduce the risk of radiation damage to normal tissues, while effectively killing the prostate cancer cells.”

To help these siRNAs target specifically on prostate cells, the investigators are turning to RNA in yet another form, called RNA aptamers — unique molecules that bind to a target, much like an antibody. RNA, like DNA, is like a twisting railroad track, made up of four building blocks called A, G, C, and U. The sequence of these blocks transmits the genetic code, and also determines how the RNA folds into a three-dimensional shape. Using technology called SELEX, Lupold and colleagues can identify RNA aptamers that bind to particular molecules, including proteins found in cancer. They have screened thousands of different RNA aptamers, and found two that bind to a cell surface protein on prostate cancer cells called PSMA (Prostate Specific Membrane Antigen). “These RNA aptamers can be synthesized and chemically connected to nanoparticles, drugs, and even siRNAs,” says Lupold. “They not only attach themselves to prostate cancer cells, but they can enter and deliver the therapeutic package inside the cell.” Several labs have used the Lupold lab’s aptamers to generate new experimental agents for the treatment and imaging of prostate cancer. “We are currently using the aptamers to selectively deliver our radiation-sensitizing siRNAs to prostate cancer cells,” says Lupold. “In our collaboration with Radiation Oncology, we hope to translate these aptamer-siRNA therapeutics for clinical trials in the next few years.” In the large multidisciplinary effort known as TEMT (for Temperature Enhanced Metastatic Therapy; see Page 18), Lupold and colleagues are using the aptamers to target iron-oxide nanoparticles to prostate tumors. This project, led by Robert Getzenberg and DeWeese, uses magnetic frequencies to heat these nanoparticles in order to make tumors more sensitive to radiation and chemotherapy. In these and other RNA-based projects, Lupold says, “we hope to learn more about how prostate cancer becomes aggressive, how we can identify the aggressive form, and how we can better treat it.”

**Digoxin: A heart drug may help prevent or treat prostate cancer**



Elizabeth Platz

Exciting new research has found that men who take digoxin, a drug used to treat congestive heart failure and arrhythmia, may have a lower risk of being diagnosed with prostate cancer. The work was led by Elizabeth A.

Platz, Sc.D., M.P.H., the Beth W. and A. Ross Meyers Scholar, and colleagues at Hopkins and Harvard, and was built on other recent Hopkins findings. (Related work on the use of statin drugs was covered in the article “Statins: Drugs that Lower Cholesterol May Help Ward off Lethal Prostate Cancer” in *Discovery* 2008).

First, scientists Jun Liu, Ph.D., Srinivasan Yegnasubramanian, M.D., Ph.D., and William G. Nelson, M.D., Ph.D., tested many

**Bottom Line:  
Digoxin Helps  
Prevent Prostate  
Cancer**

Men who regularly used digoxin at the start of the study had about a 25-percent lower risk of prostate cancer than other men. Men who took digoxin for 10 or more years had the lowest risk of prostate cancer; their risk was 40 percent lower than that of men who had never used digoxin.

These results give scientists new, prostate-specific pathways to explore in looking for new drugs to treat prostate cancer.

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

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currently available drugs — already being used to treat other health problems — on prostate cancer cells. (The great advantage to finding new uses for current drugs is that they have already been through the rigorous and time-consuming testing required by the Food and Drug Administration and similar agencies.) Their laboratory work showed that digoxin halted the growth of the prostate cancer cells. In a second study, Liu and Gregg L. Semenza, M.D., Ph.D., found some clues as to how it may work: It turns out that digoxin decreases the amount of a protein called HIF-1. “This protein signals other cells to make new blood vessels, which bring additional oxygen and nourishment to a cancer and allow it to grow even more,” explains Platz.

### Men taking digoxin have a lower risk of getting prostate cancer.

The next step was to see if digoxin protects against prostate cancer in men who take it to treat their heart problems. Platz and the Hopkins team collaborated with investigators at Harvard in charge of the Health Professionals Follow-Up Study, a group of 47,759 men who have been followed since 1986. In that study, the men, who are between 40 and 75 years old, and free of a cancer diagnosis when they first start participating, are asked every two years about the medications they take. At the start of the study, 2 percent of men said that they regularly used digoxin. By 2006, 5,008 of the men had been diagnosed with prostate cancer.

“We found that men who regularly used digoxin at the start of the study had about a 25-percent lower risk of getting prostate cancer than men who were not using the drug,” says Platz. “This was true whether they used the drug to treat congestive heart failure or arrhythmia.” Because men who have many health problems may be less likely to be screened for prostate cancer, the team also looked among men who had taken a PSA test. Again, they found that men on digoxin

had a lower risk of prostate cancer. “There was even evidence that men who took digoxin for 10 or more years had the lowest risk of prostate cancer,” Platz adds. “Their risk was 40 percent lower than that of men who had never used digoxin.”

Platz and colleagues anticipate that the results of the Hopkins studies on digoxin, when taken together, will help scientists looking for drugs to treat prostate cancer and to prevent this cancer from developing. “The digoxin work gives us new prostate-specific pathways to explore,” she says. Already, medical oncologists at Hopkins are planning a clinical trial to test the use of digoxin in men who already have prostate cancer. “This work demonstrates how when investigators from many different disciplines work together, discoveries that hold the promise of prostate cancer prevention and treatment may be made more efficiently.”

### An anti-inflammatory agent may help prevent prostate cancer from returning:

In other collaborative work, Platz and colleagues Alan Meeker, Jay Bream, Charles Drake, George Netto, Angelo De Marzo, and William Isaacs, are investigating whether a naturally produced anti-inflammatory agent, known as interleukin-10 (IL-10), can ward off prostate cancer. In previous work, they found that men who carried a particular version of the gene that makes IL-10 were less likely to develop prostate cancer — and also less likely to have the cancer come back after radical prostatectomy. “Cytokines are chemicals released by white blood cells,” notes Platz. “This particular cytokine, IL-10, by keeping down inflammation, may indirectly keep prostate cancer from becoming more aggressive.” Platz and her colleagues currently investigating this have expertise in epidemiology, pathology, immunology, molecular biology, and urology.

### Experimental Therapies Show Promise

Of all the labs at the Brady doing impressive research, the one that may be hardest to sum up easily belongs to Ron Rodriguez,

### The virus seeks out only prostate cancer cells, and then gives them a lethal cold.

M.D., Ph.D., the R. Christian B. Evensen Scholar. That’s because Rodriguez is developing experimental therapies for prostate cancer, and his investigations run the gamut from gene therapy to work with viruses, to finding new uses for drugs designed to treat other problems, to immunotherapy and cryoablation (freezing the prostate).

### New life for an old anti-seizure drug:

Rodriguez and colleagues have found that valproic acid, a drug that has been used to treat epilepsy, can slow down the progression of prostate cancer. It appears to work by inhibiting a chemical called histone deacetylase, and this, in turn, causes the cancer to become less aggressive. “We are now actively conducting a one-year clinical trial,” in which patients will be randomly assigned to take either this drug or the placebo, says Rodriguez. After one year, those in the placebo group have the option to “cross over” to the valproic acid group. “We believe this drug may have the potential to slow down the progression of prostate cancer significantly,” he continues. “In a cancer which already tends to grow slowly, this may be particularly beneficial.” Men are eligible for this trial if they have a PSA greater than 1 after a radical prostatectomy; if they have had no previous hormonal therapy; and if their PSA doubling time is less than 10 months.

### Immunotherapy and freezing cancer:

In a separate clinical trial, Rodriguez and colleagues are hoping that the combination of cryoablation — killing cancer by freezing the tissue — and immune system stimulation will generate an anti-tumor immune response throughout the whole body. This trial is intended for men with advanced prostate cancer, with at least one area of cancer available for cryoablation, and at least one other site of disease that shows up on an X-ray or other image. “We will



*Ron Rodriguez with research specialist Wasim H. Chowdhury: Their work runs the gamut from gene therapy to work with viruses, to finding new uses for drugs designed to treat other problems, to immunotherapy and cryoablation (freezing the prostate).*

perform cryoablation at the primary site of cancer, and then give intravenously a low dose of an immune-boosting drug called cyclophosphamide,” Rodriguez notes. Patients will be followed for two years, with imaging and PSA done every three months.

**Using viruses to kill cancer:** Rodriguez and colleagues have discovered that a common virus, called an adenovirus — changed

### **One challenge fighting advanced prostate cancer is simply being able to reach it all.**

slightly so that it seeks out only prostate cancer cells, and then gives them a lethal cold — can be combined nicely with high-dose radiation therapy. “This combination creates what we call a synergistic cell

kill,” Rodriguez explains. “The high-dose radiation causes the viruses to replicate more effectively in prostate cells, and this results in more effective killing of the cancer.” Rodriguez’s lab has been working on this idea for years; in earlier incarnations, the viruses required androgens (male hormones) in order to function properly. “However, the patients with the highest need, men with high-grade cancers, are typically treated with hormone therapy, and this made our viruses ineffective.” To fix this, “we discovered a way of altering our viruses so that treatment with nonsteroidal antiandrogens like casodex can activate them, and cause a synergy of prostate cancer cell death.” The scientists are currently conducting preclinical studies of these new viruses, “working out models that we intend to bring to the clinic.” Rodriguez anticipates that this approach will be combined with high-dose brachytherapy.

**When cancer is contained within the prostate, it’s much easier to cure; doctors know exactly where it is. But doctors treating advanced cancer don’t have this luxury.**

**Gene therapy:** One of the challenges of fighting advanced prostate cancer is simply being able to reach it all. When cancer is contained within the prostate, it’s much easier to cure; doctors know exactly where it is. But doctors treating advanced cancer don’t have this luxury. Thus, the best way to make sure a treatment reaches stray prostate cancer cells throughout the body is an intravenous approach — ideally, one that goes everywhere, but only affects prostate cancer cells. Rodriguez and colleagues have developed a new technology, using a particular gene on an adenovirus called the fiber gene, and specifically targeting it to a molecule on the surface of prostate cancer cells, called the PSMA molecule. This in itself is a spectacular feat of genetic engineering; many scientists have attempted it, and Rodriguez’s lab is the first to figure it out. “Everything appears to be in place for us to succeed,” says Rodriguez, “although we expect it will be an arduous process. We are nonetheless committed to finding a way to get our highly effective viral missiles to their intended target, and believe that once we have refined this targeting process, we will be able to affect diffuse disease in a major way.”

[continued from page 10]

might depend on knowing if his cancer has progressed. For men on active surveillance, a yearly biopsy is important. It is the best way to identify cancer progression in time for curative treatment.” For the greatest accuracy, the Hopkins investigators now recommend a 14-core biopsy (instead of a biopsy that takes only 12 samples), which includes two biopsies from the area of the prostate located the farthest from the rectum. This study was presented at the 2009 Annual Meeting of the American Urological Association.

### PCA3:

## New Marker Shows Promise as Helpful Urine Test for Prostate Cancer

As wonderful and life-saving as the PSA test has been in detecting prostate cancer early, urologists and patients have wrestled with it, because many men with an elevated PSA have negative biopsies, may not have cancer, and shouldn't have to be subjected to repeated biopsies. Other conditions, including benign enlargement (BPH), can raise a man's PSA; it is far from being a purely cancer-specific blood test.

**“We urgently need a marker that is truly negative when cancer does not exist.”**

This is why Alan Partin, M.D., Ph.D., Urologist-in-Chief, has worked so hard to find and evaluate a better test. “We urgently need a marker for prostate cancer that's more specific; in other words, a test that is truly negative when cancer does not exist,” he says. Recent studies in the U.S and Europe have identified genes that are found in prostate cancer cells but not in normal prostate cells. Among them is a messenger RNA called PCA3, a particular form of RNA, which was discovered and first reported in 1999 by Brady scientists William Isaacs, Ph.D., the William



Isaacs and Partin: Hoping to reduce unnecessary biopsies.

Thomas Gerrard, Mario Anthony Duhon and Jennifer and John Chilsty Professor of Urology; Marion Bussemakers, Ph.D.; and Jack Schalken, Ph.D.

“PCA3 is highly expressed in prostate tumors, but not in normal or BPH prostate tissue,” says Partin. “Over the last decade, the work of these Brady investigators, in conjunction with scientists from other academic institutes and industrial collaborators in Canada and the United States, has provided us with a reliable urine test for prostate cancer that has great clinical promise.”

In early trials, the PCA3 urine test proved able to detect prostate cancer nearly 70 percent of the time. Importantly, it also had a “negative predictive value” — which means it accurately reported that cancer was not present — of 90 percent. “This test has great potential to reduce the number of unnecessary invasive diagnostic procedures done each year,” says Partin. “It has also shown some ability to discriminate among men who would benefit from a second biopsy, when a first biopsy showed no evidence of cancer.”

“Although these initial results are very promising, further validation is necessary and under way to understand fully the clinical usefulness of this test,” adds Partin. His research group is participating in an National Cancer Institute funded, multi-institutional clinical trial of the PCA3 urine test. If the results from these and other studies live up to the biomarker's promise, the PCA3 test will be headed toward being approved by the Food and Drug Administration for widespread use.

### SHORT TELOMERES:

## Why Some Men Are More Likely to Develop Prostate Cancer

As any respectable crossword puzzle fan knows, the little tip at the end of a shoelace is called an aglet. Similarly, as genetic scientists know, there are little tips at the ends of every chromosome. They're called “telomeres,” and like aglets, they keep strings from fraying, although they're a bit more complicated than the simple plastic shoelace covers; telomeres are made up of long stretches of specialized DNA.

“Unfortunately,” says scientist Alan Meeker, Ph.D., “every time a cell divides, a portion of the telomere's DNA is lost. Thus,

**“Every time a cell divides, a portion of the telomere's DNA is lost. Thus, as we age, our telomeres progressively get shorter.”**

as we age, our telomeres progressively get shorter.” From previous work, Meeker and colleagues including Don Coffey have come to believe that this shortening of telomeres is an important contributing factor to the development of prostate cancer. Every time the buffer between a chromosome and the outside world shrinks, it is that much more vulnerable to injury.

As part of nature's luck of the draw — the genetic blessings and hindrances all of us are born with, through no fault or virtue of our own — some men are fortunate enough to be born with long telomeres; others are born with shorter ones. “In fact, variations in telomere length are inherited,” says Meeker. This made him wonder: Do men who inherit short telomeres have a higher risk of developing prostate cancer?

In a recent study, he and colleagues used a simple blood test to find out. They measured telomere length in 127 people from 17 families who are part of the Johns Hopkins

Hereditary Prostate Cancer family registry. “We found that in 10 of these families, the average telomere lengths were shorter in men with prostate cancer when compared to their unaffected family members,” says Meeker, and this finding has exciting implications that may help in early diagnosis. “We believe that measuring telomere length, with a blood test, in men with a strong family history may help determine their risk of developing prostate cancer.” Men found to be at risk, he adds, could receive targeted interventions aimed at trying to slow down the rate of telomere loss, or at preventing further growth of prostate cells.

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## Potent Men Live Longer After Radical Prostatectomy

Erectile dysfunction (ED) and cardiovascular disease are often linked; in fact, ED has been recognized as one of the early warning signs of heart trouble. There are several reasons why the two often seem to go together: One is that the same buildup of plaque that causes the arteries to narrow in heart disease can hinder blood flow to the penis; so can some hypertension medications — which do such a good job of lowering blood pressure that they don’t allow the blood flow necessary for erection; and depression, which often accompanies heart disease, may be still another reason why these two conditions are linked.

**Many men with erectile dysfunction lived more than 20 years after their surgery.**

In a recent study, Brady scientists Misop Han, M.D., and Patrick C. Walsh, M.D., investigated whether ED has any association with how long men live after radical prostatectomy. Would men who were potent before surgery, they wondered, live longer than men who were experiencing ED before surgery? To find out, Han studied the before-and-after potency information of

more than 2,500 men, all Walsh’s patients, who had undergone radical prostatectomy at Hopkins (from a resource pool of available information on than 3,500 men who underwent surgery performed by Walsh during the study period).

“We discovered that men who were potent before surgery lived significantly longer than men who were not,” says Han. For example, at 20 years after surgery, 69 percent of potent men were alive, but only 52 percent of the men with ED were alive. Walsh notes that potency before surgery did not affect men’s survival from prostate cancer: in other words, men with ED were just as cancer-free after surgery as potent men.

Han, the study’s leader, believes that the men who were potent probably lived longer because they were younger and healthier when they underwent surgery. “However,” he points out, many men with erectile dysfunction lived more than 20 years after their surgery.” He adds that lifestyle changes — getting in better shape in general, by exercising, eating better, and losing excess weight — can improve potency, and “men who better their overall health may improve their life expectancy, as well.”

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## When Can You Stop Checking Your PSA?

We know when screening should start. All men, especially African American men, and men with a family history of the disease, should have their first PSA blood test, and digital rectal exam at age 40. This is to establish a man’s baseline PSA; this number, and how fast it changes, will determine how often he needs to come back for further screening. But when can a man stop getting his PSA checked?

“This has been a more difficult question to answer,” says urologist Edward M. Schaeffer, M.D., Ph.D., “and many urologists have made recommendations to patients with little hard data to go on.” In fact, many men in their late seventies and older continue to undergo PSA screening, and this could lead to unnecessary treatment and complications; men that age are more likely to die from something other than prostate cancer.

**Many men in their late seventies and older continue to undergo PSA screening, and this could lead to unnecessary treatment and complications.**

To begin to answer this question, urologists Schaeffer and H. Ballentine Carter, M.D., worked with investigators from the Baltimore Longitudinal Study of Aging. They studied the PSA measurements of more than 800 men as they aged, and found that for men over 75 with PSA less than 3 ng/ml, none died of prostate cancer and only one developed aggressive, high-risk prostate cancer. In contrast, men of all ages with a PSA of 3 or higher had a continually increasing risk of dying from prostate cancer. “Based on these findings,” notes Schaeffer, “we believe that all men with a PSA higher than 3.0 should continued to be screened, and that men over age 75 with a PSA lower than 3.0 may choose, after consultation with their urologist, to discontinue PSA testing and be followed with exams and clinical histories. Our study suggests that men at an age of 75 to 80 years who have a PSA level below 3 are unlikely to be diagnosed with a high-risk prostate cancer.”

## Bottom Line: When to Say Goodbye to PSA Testing?

Of men over 75 with PSA less than 3, none died of prostate cancer and only one developed aggressive, high-risk prostate cancer.

In contrast, men of all ages with a PSA of 3 or higher had a continually increasing risk of dying from prostate cancer.

## The “Hottest” New Approach for Killing Prostate Cancer

Hopkins scientists, led by Robert H. Getzenberg, Ph.D., and Theodore L. DeWeese, M.D., are developing a new way to make hidden, metastatic prostate cancer cells more sensitive to effective treatment.

**Heat weakens a cancer cell, undermines its internal structure, and makes it ripe for further therapy.**

Their novel approach — called TEMT, for Thermal Enhanced Metastatic Therapy — may have found cancer’s Achilles heel: Heat.

Heating cancer cells makes them vulnerable. It’s like opening a window or, if you were watching a movie like “Star Wars,” temporarily lowering the enemy’s force field. Weaken the cancer cells, and then go in for the kill, with radiation, chemotherapy, or immunotherapy: Heat makes cancer much more susceptible to all three approaches.

This concept started when Don Coffey, Ph.D. (see Page 1), was inspired by what happened to cyclist Lance Armstrong. Armstrong nearly died as a young man, because his body was riddled with advanced cancer; testicular cancer had spread to his brain, liver, and elsewhere. For years, Coffey has marveled at Armstrong’s recovery, as he has tried to understand how it happened. Not only was Armstrong’s cancer cured, he recovered well enough to win the grueling Tour de France seven times. The secret, Coffey believes, was heat — which testicular cells don’t tolerate well at all. This is why the testicles are separate from the body; the slight distance keeps them cooler, below normal body temperature. Because testicular cells are already more sensitive to heat, when they move inside the body as the cancer spreads, they’re that much weaker, and easier to kill.

It turns out that heating a cell changes the organization of DNA, and undermines its internal structure as well as modifying the nuclear matrix (which Coffey discovered years

ago). “It appears that we can increase the efficacy of the currently utilized treatments for metastatic cancers,” says Getzenberg, the Brady’s research director. He and DeWeese, Chairman of Radiation Oncology and Molecular Radiation Science, along with scientists Shawn Lupold, Ph.D., Prakash Kulkarni, Ph.D., and others are exploring the molecular mechanisms that underlie these amazing examples of healing. Their work has revealed a new physical approach to cancer that permits the direct delivery of ultra-precise, low levels of heat to cancer cells. They have found a temperature that makes the cancer cells ripe for further therapy.

Lupold (see Page 12) synthesized RNA homing molecules — think of microscopic, heat-sensitive missiles — that can direct tiny heating elements directly to the surface of the prostate cancer cells. “These extremely small elements are high-tech iron nanoparticles,” explains Getzenberg. “A pioneer in how to heat these particles, by using external magnets, is a new faculty member, Robert Ivkov.” Ivkov, Ph.D., is a biophysical chemist in Radiation Therapy and Molecular Radiation Sciences. “We can all be excited as this expert team tunes this new therapeutic approach to seek and destroy hidden nests of metastasis in men with advanced prostate cancer.”

### Bottom Line: Heat Weakens Cancer

Heat makes hidden, metastatic prostate cancer cells more sensitive to radiation, chemotherapy, and immunotherapy.

## Two Agents Show Promise as Nerve-Protectors

The problem is the nerves. They sit on either side of the prostate, and they are responsible for erection. They’re a surgeon’s nightmare — so tiny and fragile, and so easy to damage

during radical prostatectomy.

Neuro-urologist Arthur L. Burnett, M.D., M.B.A., a surgeon who also studies these nerves, has been searching for a neuroprotective “holy grail” — an agent that will not only protect these nerves during the trauma of treatment, but that will nurture them, strengthen them, and maybe even invigorate them, as well. In this quest, he has found two candidates that look promising.

One is known familiarly as “Epo,” for erythropoietin, a versatile hormone naturally made in the kidney that stimulates production of red blood cells; it also helps people with anemia. “Erythropoietin has been shown to preserve nerve function after injury,” says Burnett. His preliminary studies of men who have received erythropoietin after radical prostatectomy, published in the *Journal of Sexual Medicine*, suggest that it may indeed be beneficial in promoting the recovery of erectile function. Unfortunately, his study in men undergoing surgery was temporarily put on hold by a nationwide alert

**The “holy grail” here is an agent that will not only protect these nerves during the trauma of treatment, but that will nurture, strengthen, and maybe even invigorate them.**

from the Food and Drug Administration, which is looking into safety issues before allowing any investigators to proceed.

The other promising drug is called Losartan. It’s already used to treat hypertension, and “It has been shown to maintain the health of blood vessels,” says Burnett. Scientifically, it is an angiotensin II type I receptor antagonist agent. In laboratory studies, it has been shown to enhance erection recovery and limit penile deformity and scarring in rats. Burnett believes it may help preserve penile health in men after radical prostatectomy, and he is conducting pilot clinical studies to investigate this possibility.

## RECENT HONORS AND AWARDS

Once again — this makes 19 years in a row — the Johns Hopkins Hospital and the Brady Urological Institute were ranked as the number one hospital and number one urological center by *U.S. News & World Report* magazine. This continued recognition is a tribute not only to our physicians and scientists at the Brady, but also, in very large part, to the impeccable care of the nursing staff and excellence of our support staff. We are so proud of all of these individuals, who all should be congratulated for their dedication to providing the very best patient care. Also, the Brady came out on top in an article on the 100 most-cited articles in urology. Johns Hopkins had the most cited papers, 13. Harvard, Stanford, and the University of California came next, each with five cited papers. It was especially nice for us to see that of the five most-cited authors, all were either on the faculty of the Brady or had trained here — again, a wonderful testament to the lifelong dedication of the Brady to excellence and discovery.

**Arthur Burnett, M.D.**, earned a M.B.A. in Medical Services Management from the Johns Hopkins University's Carey Business School. He also received the Carey Business School's Edward J. Stegman CPA Memorial Award.

**Michael Carducci, M.D.**, has been named the AEGON Professor of Prostate Cancer Research.

**Misop Han, M.D.**, and Dan Stoianovici, Ph.D., received the Best Paper Award from the Engineering and Urology Society for their project, "Tandem Robot-Assisted Laparoscopic Radical Prostatectomy."

**John Isaacs, Ph.D.**, received the Meritorious Achievement Award from the Society For Basic Urologic Research.

**Shawn E. Lupold, Ph.D.**, the Phyllis and Brian L. Harvey Scholar, received the Young Investigator Award from the Society for Basic Urologic Research.

**William G. Nelson, M.D., Ph.D.**, Professor of Urology, Pharmacology, Medicine, Pathology, and Radiation Oncology, with a joint appointment in Environmental Health Sciences at the Bloomberg School of Public



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Health, has been named the Marion I. Knott Professor of Oncology and Director of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. He is also the Principal Investigator for the National Cancer Institute (NCI)-funded Molecular Targets Training Program, dedicated to providing clinical oncology fellows specific training in translational research, and for the NCI-supported Prostate Cancer SPORE Program, a multidisciplinary research effort for translational research targeting new approaches to prostate cancer detection, diagnosis, prevention, and treatment. (For more on SPORE, see Page 7.)

In announcing the appointment, which followed a national search, Edward D. Miller, Dean of the Medical Faculty and chief executive officer of Johns Hopkins Medicine, said that Nelson "has the energy and talent to ensure the cancer center's continued success as a leader in discovery and patient care,

but also to face the scientific and administrative challenges that science and health care delivery face in the 21st century."

**Edward M. Schaeffer, M.D., Ph.D.**, received several awards recently, including the Howard Hughes Medical Institute Physician Scientist Early Careers Award, the American Urological Association/Astellas Rising Star in Urology Award, the Passano Foundation's Clinician Scientist Award, and a Clinician Scientist Award from Johns Hopkins.

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

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