

DISCOVERY

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A lavish dinner was held at the Belvedere Hotel in Baltimore to dedicate the Brady Institute. Keepsake Centennial Section Inside!

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“A MAJOR GAME-CHANGER” FOR MEN WITH METASTATIC PROSTATIC CANCER

New study proves early treatment with both chemotherapy and hormonal therapy has a major impact.

It used to be that men with metastatic prostate cancer were started on hormonal therapy, and when cancer escaped the hormones they moved on to chemotherapy. By then, there was so much cancer, and the disease had evolved into something so difficult to kill, that the response to this treatment was usually short-lived. A decade ago, investigators from the Eastern Cooperative Oncology Group Genitourinary Group (ECOG), chaired by Hopkins oncologist Michael Carducci, decided that it was time to shake things up. What if, they wondered, instead of waiting for the disease to come to us, we go after it sooner, rather than later?

Results of a new study called CHARTED, sponsored by the National Cancer Institute, have proven that early treatment with chemotherapy in addition to hormonal

therapy has a major impact on quality and quantity of life. This study showed that in men with more than three metastatic lesions on bone scan, when chemotherapy is given at the same time as hormonal therapy is started, survival improved by nearly a year and a half.

“This has the potential to be a major game-changer,” says Carducci. He and Eisenberger were co-authors of this study, led by Christopher Sweeney of the Dana Farber Cancer Institute/Harvard Cancer Center. “Based on these results, it seems now that men diagnosed with metastatic disease will do well to include a medical oncologist in their care team to seek the advisability of early chemotherapy, in addition to hormonal therapy.”

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Partin: Urology began here at the Brady.

A CENTURY OF LEADING THE WAY

From 1915 to 2015:
continuing on the
path of innovation
and *Discovery*

The year 1915 marked a first in American medicine: the opening of the Brady Urological Institute. Never before had there been a freestanding hospital dedicated solely to the field of Urology. For that matter, the field of Urology as a surgical specialty was invented at Johns Hopkins by a surgeon and scientist named Hugh Hampton Young. Young's accomplishments would fill up these pages, but you can read the highlights in our special Centennial section. You can also read how we got our name — from our benefactor, James Buchanan “Diamond Jim” Brady, whose generous donation made this Institute possible.

As usual in this issue of *Discovery*, you will get a glimpse at the incredible volume, breadth and depth of our research on prostate cancer, our innovations in treatment, and our work toward preventing prostate cancer from ever developing. And finally, you may notice that our name has changed: Instead of *Prostate Cancer Discovery*, this is simply, *Discovery*. From now on, we will be bringing you advances in our work related to other genitourinary cancers. For example, you can read about our innovative program for watchful waiting on small kidney cancers, our minimally invasive surgery program and our surgeons who routinely do something very few surgeons in the world do — remove part of the kidney, which removes cancer but saves the kidney and dramatically minimizes complications. And you will see another first: A new Institute dedicated to bladder cancer, the Johns Hopkins Greenberg Bladder Cancer Institute, made possible by the generosity of Erwin L. Greenberg and Stephanie Cooper Greenberg.

In a century, Johns Hopkins has created and continued to transform the field of Urology. We look forward to our next century with great excitement and hope.

Best wishes,

ALAN W. PARTIN, M.D., PH.D.
David Hall McConnell Professor and Director
The Brady Urological Institute

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This work, presented during the plenary session of the 2014 American Society of Clinical Oncology, found that six cycles of chemotherapy with docetaxel given together with standard hormonal therapy extended the lives of men with newly diagnosed metastatic prostate cancer by nearly 18 months, with manageable side effects. “We saw the benefits mainly in men with high-volume metastasis,” says Eisenberger, “men with more than three lesions seen on a bone scan, and/or liver and lung involvement.”

It is well known that prostate cancer cells are sensitive to hormonal therapy, says Carducci, “but in the vast majority of men, for many reasons, the cancer continues to grow.” In fact, scientists speculate that even at the time of diagnosis, some cancer cells are already hormone-resistant.

“The idea behind CHARTED,” adds Eisenberger, “was that if docetaxel is effective against cells that no longer respond to hormones at late stages, then it could be even more effective

if we gave it early, when there are far fewer hormone-insensitive cells around. The results strongly support this hypothesis.” Interestingly, 10 years ago, Eisenberger co-chaired the global study of docetaxel, which found that the drug extended life in men with advanced cancer – after they had already become resistant to hormonal therapy. Given earlier, the drug shows even more promise now, he believes.

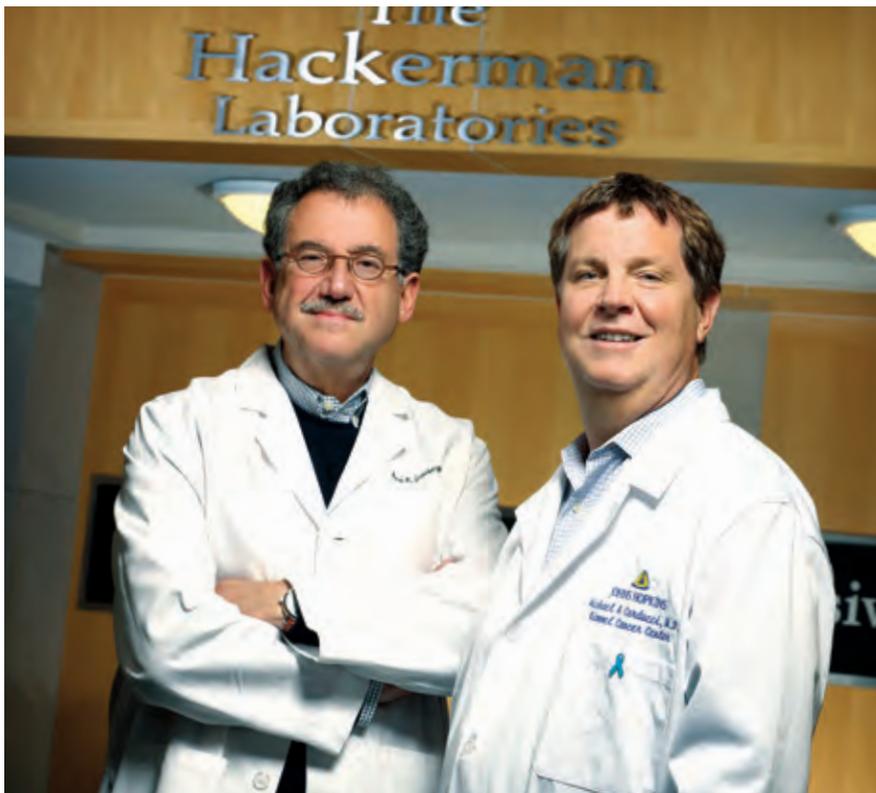
“Based on these results, it seems now that men diagnosed with metastatic disease will do well to seek the advisability of early chemotherapy, in addition to hormonal therapy.”

Giving chemotherapy sooner, rather than later, prolongs life for men with metastatic disease. ■

New Test Can Determine Whether Expensive Treatments Will Work In Metastatic Cancer

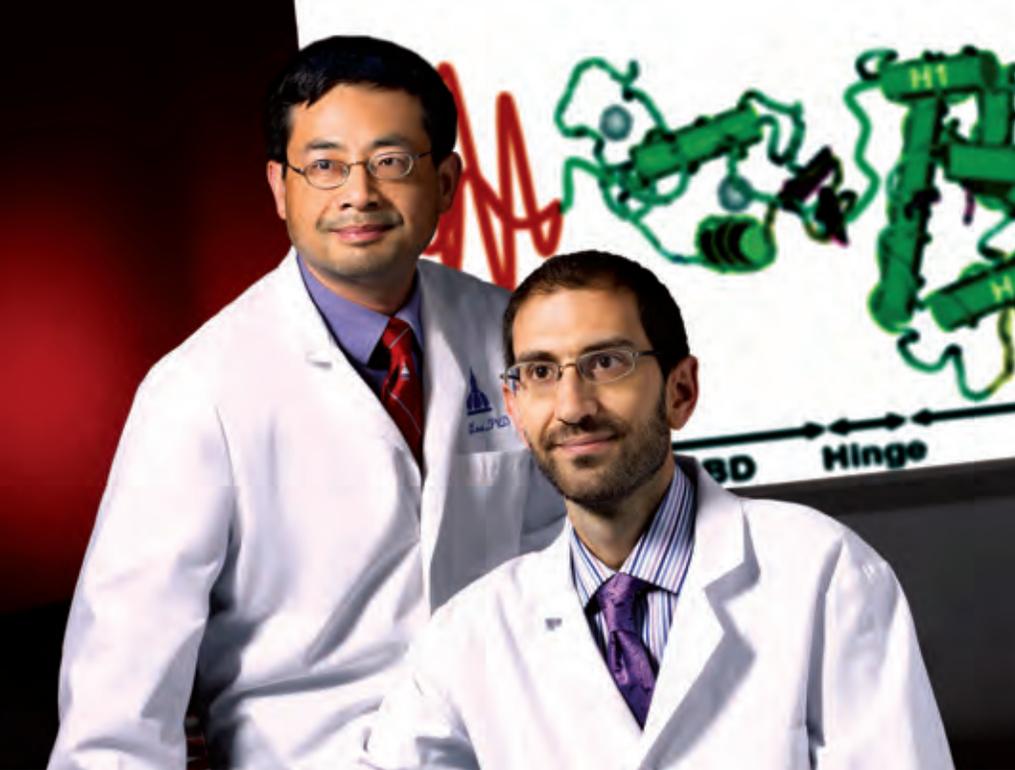
For men with metastatic prostate cancer that is growing despite hormonal therapy, there are two drugs that can help: enzalutamide and abiraterone. However, they are very expensive — costing as much as \$100,000 a year — and not every man responds to either drug. Until now, the only way doctors could determine which one of these drugs to use was to prescribe one and see if it worked, and if it didn't, to try the other. But thanks to groundbreaking research led by Brady scientists Jun Luo, Ph.D., Emmanuel Antonarakis, M.D., and colleagues, there is now a simple blood test that can save these men time and money, and can point the way to more effective therapy. This important study was published in September in the *New England Journal of Medicine*.

“Although both of these drugs treat metastatic castrate-resistant disease, they each work a little differently,” says Luo. “Enzalutamide targets the androgen receptor directly, and abiraterone is something called an androgen synthesis inhibitor; it diminishes the amount of androgen that can bind to the androgen receptor.” Resistance to both of these pricy drugs has been observed, “but the reason for this resistance was unclear,” until the Hopkins scientists found the common thread on the molecular level. For years, Luo has studied variants of the androgen receptor that bypass the usual mechanisms of activation; they lack the proper binding site for androgen. A particular androgen receptor variant, called AR-V7, is associated with resistance to both drugs, and Luo, Antonarakis, and colleagues have developed an assay to look for AR-V7 in the blood. Antonarakis recently presented their results at the American Society of Clinical Oncology's annual meeting in Chicago.



Eisenberger and Carducci: Giving chemotherapy sooner rather than later prolongs life..

Continued on page 4 »



Luo and Antonarakis: Blood test could save men the trouble and expense of trying a drug that won't work.

“Because the turn-around time for this assay is only about three days, we believe that this test could be readily used in the near future for any patient who is contemplating therapy with enzalutamide or abiraterone. If they test positive for AR-V7, these men could potentially be steered toward alternative treatments, such as immunotherapy, chemotherapy, or radiotherapy.”

Continued from page 3 »

In the study, nearly 39 percent of 31 men taking enzalutamide and 19 percent of men taking abiraterone had detectable AR-V7 in the prostate cancer cells circulating in their bloodstream. “Of the men on enzalutamide, those who were AR-V7-positive had poorer PSA response rates compared to the others,” says Antonarakis. “They also had shorter progression-free survival compared to men with no detectable AR-V7.” Similarly, men with detectable AR-V7 levels who were taking abiraterone did not have as much of a drop in their PSA as other men, and they, too, had shorter progression-free survival. To make sure that AR-V7 was the key, Luo and Antonarakis adjusted their analysis to account for numerous other factors, and found that the men who were AR-V7-positive had “independently inferior responses to the two drugs” than men whose blood showed no AR-V7.

Luo and Antonarakis also tested blood from the men during and after their therapy with enzalutamide and abiraterone, and found that some men — six out of 42 — who had been AR-V7-negative before treatment changed during the course of therapy and became AR-V7-positive. “These men had intermediate clinical

outcomes,” Luo says, “better than those who started out as AR-V7-positive, but worse than those who remained AR-V7-negative during treatment.

The scientists also found that AR-V7 was relatively common among men with metastatic, castrate-resistant prostate cancer. Before this study, “it was thought that the prevalence of AR splice variants was very low,” says Antonarakis. “But we showed that the prevalence of AR-V7 actually increases after treatment with abiraterone and enzalutamide.” The variant is present in about 12 percent of men who have not received either of these drugs, he adds, “but it appears in about 67 percent of men after exposure to both abiraterone and enzalutamide.”

AR-V7 was first discovered by Luo in 2008, but at that time, scientists did not recognize the clinical significance of androgen receptor splice variants. “This study is the first to suggest that AR-V7 can be used as a predictive marker in men with advanced prostate cancer,” Luo says. “If these preliminary findings are replicated by other groups using a larger number of patients, AR-V7 could eventually be used as a biomarker to predict primary or acquired resistance to androgen pathway-targeted therapies.” Much additional work needs

to be done, he adds. “First, we will need to validate our assay, incorporating the test into larger, prospective therapeutic trials of both abiraterone and enzalutamide.” In other research, the investigators plan to study the role of AR-V7 in predicting resistance to chemotherapy in prostate cancer patients.

“Because the turn-around time for this assay is only about three days, we believe that this test could be readily used in the near future for any patient who is contemplating therapy with enzalutamide or abiraterone,” says Antonarakis. “If they test positive for AR-V7, these men could potentially be steered toward alternative treatments such as immunotherapy, chemotherapy, or radiotherapy.”

This research was supported by the Prostate Cancer Foundation. Additional authors on the study included Changxue Lu, Hao Wang, Brandon Lubber, Mary Nakazawa, Jeffrey C. Roeser, Yan Chen, Helen L. Fedor, Tamara L. Lotan, Qizhi Zheng, Angelo M. De Marzo, John T. Isaacs, William B. Isaacs, Rosa Nadal, Channing J. Paller, Samuel R. Denmeade, Michael A. Carducci, and Mario A. Eisenberger. ■

Molecular-Genetic Imaging Shows Individual Prostate Cancer Cells

Knowing cancer is out there, but not knowing where, has long frustrated doctors and men who have cancer that has spread beyond the prostate. Now Hopkins scientists have developed a new imaging method that specifically targets cancer cells. The method involves injecting a nanoparticle sensor that “only becomes activated when it encounters malignant cells, explains radiologist Martin Pomper, M.D., Ph.D., “but not normal tissue, so that cancer and its metastases can be detected anywhere in the body.” The method has performed well in imaging studies of mice with metastases, including those due to prostate cancer.

This work, which has been published in *Nature Medicine* and *Cancer Research*, is based on years of research into the genes and transcription factors that make malignant cells different from normal cells. “To image the cancer, after injecting the nanoparticle sensor, we also inject an imaging agent to detect the genes turned on by the cancer.”

Pomper and colleagues have also designed imaging agents that bind to prostate-specific membrane antigen (PSMA), a marker for prostate cancer. A clinical trial with the first-generation nanoparticle-sensor is in the planning stages, while the first- and second-generation PSMA-targeted imaging agents recently have completed first-in-human studies. ■

Study Upturns Ideas About a Key Molecule in Advanced Prostate Cancer

Research by Brady pathologists has added an important new piece to the puzzle of the immune system’s role in prostate cancer. Even better, it suggests a potential new target for treatment of metastatic disease.

The key player in this discovery is Interleukin-6 (IL-6), a cell signaling molecule that normally is involved in the body’s immune response to bacterial infections and other conditions. “Early evidence for a role for IL-6 in the development and progression of prostate cancer came from studies examining levels of this molecule in the blood of men with metastatic or hormone-refractory prostate cancer,” says Karen Sfanos, Ph.D., Assistant Professor of Pathology and Oncology. “Studies consistently showed that elevated blood levels of IL-6 were associated with poor prognosis.” Higher levels of IL-6 may also serve as a marker of other problems connected to advanced prostate cancer, such as weight loss and fatigue. Anti-IL-6 drugs, such as siltuximab, have entered into clinical trials, but so far have not proven as helpful as scientists had hoped.

A recent study conducted by Shu-Han Yu, M.S., a Pathobiology graduate student in the laboratory of Sfanos and Angelo De Marzo, M.D., Ph.D., may shed new light on the role of IL-6 in the development and progression of prostate cancer. It may also help scientists come up with better ways to target this molecule in metastatic disease.

The study set out to answer some important questions about IL-6 in men with advanced prostate cancer, Sfanos says, including: “Precisely when during disease development and progression is IL-6 made, and what specific cell types are responsible for its production? Does IL-6 come from prostate tumor cells, or from other cells?” Until recently, these questions were difficult to assess.

Because the IL-6 protein is rapidly secreted, measuring it was like trying to hit a moving target. In this study, “Shu-Han used a cutting-edge technology called chromogenic in situ hybridization,” Sfanos explains. “This is an assay that can detect IL-6 genetic material called RNA within a cell before it is made into the IL-6 protein that is secreted from the cell. Surprisingly, Shu-Han discovered that IL-6 is not made by prostate cancer cells in either primary or metastatic disease. These findings are in stark contrast to previously published literature.”

It turns out that IL-6 is not made by prostate cancer cells in either primary or metastatic disease.

“These findings are in stark contrast to previously published literature.”

It turns out that IL-6 is made by cells in the stroma, the supportive framework of cells surrounding the tumor, and is produced by immune cells and cells called endothelial cells that are contained in blood vessels. “Intriguingly, we found that in metastatic disease, IL-6 production in endothelial cells was distinctly associated with blood vessels in prostate cancer metastases to bone, as opposed to metastases at other anatomical sites. This might represent a unique mechanism by which IL-6 is involved in prostate cancer progression.” It might also lead to new ways to target this molecule, and alleviate some of the worst symptoms of metastatic cancer. Other Hopkins investigators involved in the study include Qizhi Zheng, M.D., Jun Luo, Ph.D., and Emmanuel Antonarakis, M.D. ■

Making Active Surveillance Safer

“Our infectious disease experts have helped us develop an approach to repeat prostate biopsies that is safer for men in active surveillance, and also for men undergoing routine prostate biopsies for an elevated PSA.”

Active surveillance, in carefully selected men, can prevent unnecessary treatment of prostate cancer. However, this approach is not without potential side effects. “Men on surveillance need periodic prostate biopsies for disease monitoring, and a major risk of prostate biopsy is infection,” says urologist H. Ballentine Carter, M.D.

To get a needle into the prostate, a urologist needs to go through the rectum; there is a risk that a biopsy-related infections can develop if bacteria in the rectum, such as *E. coli*, find their way to the prostate and, eventually, the bloodstream. To prevent this, urologists administer an antibiotic called a fluoroquinolone (Ciprofloxacin) before and after the procedure. However, says Carter, it has become evident that about one out of five men has fluoroquinolone (FQ) resistance — which means that an infection could develop that might be more difficult to treat. “Two and a half years ago at the Brady we began a program to test, using a simple rectal swab sample, whether or not men have FQ resistance before biopsy. With this information, we can select the best antibiotic to prevent infection.” In the Hopkins Active Surveillance Program, men have been getting these rectal swabs every six months and now Carter has new information on how resistance develops over time.

Jason Cohen, a Hopkins medical student who has studied these swabs, found that diabetes is a risk factor for FQ resistance. He also identified a substantial number of men with *E. coli* who are resistant to other antibiotics commonly used to prevent post-biopsy infections. “This study, for the first time, evaluated the longitudinal patterns among men with repeat rectal swabs,” says Carter. “Two of three men who harbored resistant organisms maintained this resistance on a follow-up

swab six months to a year later, and 9 percent of those who had no resistant organisms developed a resistant organism at the second swab.” Multiple biopsies were not associated with increased FQ resistance, he adds. Using these data, “our infectious disease experts have helped us develop an approach to repeat prostate biopsies that is safer for men in active surveillance, and also for men undergoing routine prostate biopsies for an elevated PSA.”

Lowering the risk of misclassifying cancer: “Misclassification is the problem of relying on a prostate biopsy, which samples only a small fraction of the prostate, to reflect the biology of the entire gland,” says Carter. “If a diagnosis of low-grade prostate cancer is made on prostate biopsy and a patient chooses active surveillance, the risk that a higher-grade, more aggressive cancer is present within the prostate can range from 10 to 30 percent.” A new technique called multi-parametric magnetic resonance imaging (mpMRI) could lower the risk by helping select which men truly have low-grade cancers; it could also reduce the number of prostate biopsies needed by men on active surveillance.

HERE'S HOW IT WORKS: MRI uses a magnetic field to form images of the body, and mpMRI identifies prostate cancers based on three characteristics of cancerous tissue:

- Abnormal signals that emanate from prostate tissue after exposure to a strong magnetic field;
- High cellular density and disorganized tissue architecture, leading to abnormal diffusion of water molecules within tissue; and
- New blood vessel formation, which creates abnormal perfusion of contrast within tissues.

By assessing all three of these parameters, mpMRI can detect prostate cancers that were missed on a prostate biopsy, particularly tumors arising from sites that are not commonly sampled, such as the anterior area of the gland.

In a study of men on active surveillance, “our group demonstrated that when mpMRI suggested the absence of prostate cancer in a particular area of the prostate, there was a high probability that cancer was absent on multiple biopsies taken from these negative mpMRI areas,” Carter explains. Carter, with Sayed Dianat, a radiology fellow, and Kasia Macura an MRI expert, recently studied 96 men who met the strictest criteria for entering the Hopkins Active Surveillance program and had an mpMRI within one year of entering the program. In follow-up biopsies, “we found cancer in 8 percent of those without any abnormality on the baseline mpMRI, as compared to cancer in 41 percent of those who showed an mpMRI abnormality on their baseline scans.” The scientists concluded that men without any mpMRI abnormality have a 65- percent lower likelihood of “a positive follow-up prostate biopsy that would have triggered prostate cancer treatment. We are now using mpMRI routinely to help select the most appropriate candidates for active surveillance, and to help reduce the frequency of prostate biopsies.”

New technology is also making it possible for the team to merge the mpMRI with a live ultrasound image, “so that during a prostate biopsy, specific areas within the prostate that are abnormal on mpMRI can be targeted,” Carter says. ■



Laiho: BMH-21 kills cancer, spares normal cells.

Promising Molecule May Become Anti-Cancer Drug

Several years ago, Marikki Laiho, M.D., Ph.D., and her research team were screening a host of molecules, looking for ones with potential to fight cancer. They found one that looked promising against prostate cancer, called BMH-21. “This molecule stood out by its novelty and great potency to kill cancer cells,” says Laiho. But because the chemical makeup of this molecule was new, “exactly how it was able to exert its anticancer while sparing the normal cells was unknown.”

Over the last year, Laiho, Professor of Radiation Oncology and also of Oncology, and her team found BMH-21’s target: RNA polymerase I transcription. “This is a key transcription program that drives the production of building blocks for cellular protein synthesis,” says Laiho. “In most cancers, this is on overdrive. Yet even though the deregulation of this molecule is so common in cancer, no one has ever explored this as a potential form of therapy.”

Laiho’s team showed that when BMH-21 was used to treat cancer cell lines grown in culture or in mouse tumors, it proved “highly effective and led to suppression

of cancer cell growth, by rapid and profound repression of RNA polymerase I transcription in a unique fashion.” Even though BMH-21 binds DNA, it had an anti-cancer effect without causing damage to the DNA itself, which is not something that can be said of conventional chemotherapy drugs.

The team has since identified other novel structural variations of the parent molecule, which together with a recently granted patent will support the development of the molecule to a clinical agent. “We believe that BMH-21 has particular relevance for the treatment of prostate cancers.” This research was published in *Cancer Cell*, the *Journal of Medicinal Chemistry* and the *Oncotarget*. One more article for the journal *Molecular Cancer Therapeutics*, is in press.

For this work, Laiho’s team was awarded the 2014 Prostate Cancer Foundation Global Challenge Award, which will allow the scientists to pursue the activity of BMH-21 in models of advanced prostate cancer. Laiho, the principal investigator, is working with co-investigators at Johns Hopkins and the University of Maryland: Angelo De Marzo, Charles Bieberich, Srinivasan Yegnasubramanian, Sarah Wheelan, and Paul Sirajuddin. ■

First-Ever MRI Robot Targets Potential Cancer Sites for Biopsy

Here’s a challenge: MRI is getting really good at imaging localized prostate cancer, and although prostate biopsies have traditionally been done using another form of imaging, transrectal ultrasound, there are now ways to “fuse” these two technologies in real time, for a more comprehensive picture of the prostate while a biopsy is under way. But the two forms of technology don’t always go together perfectly, and sometimes this can make it difficult for the urologist to target with the ultrasound-guided biopsy needle the suspicious lesions that the MRI has picked up. Another problem: Because MRI requires that the patient lie inside

a doughnut-shaped machine, the biopsy must be done using a special device. Also, there can be no electricity inside the MRI room.

Dan Stoianovici, Ph.D., Director of the Johns Hopkins Urology Robotics Program and Laboratory, has overcome these obstacles and developed a pneumatic-driven robot that has absolutely no metal — metal and the strong magnetic field inside the MRI wouldn’t work well together — and is made of plastic, ceramic, glass, and rubber, “all non-magnetic and non-conducting materials,” he notes. “The robotic device mounts on the MRI table alongside the patient. The physician selects a suspicious region that the MRI has shown, and the robot automatically guides the needle to the target and presets the depth of insertion.”

The device has been approved and declared MRI-safe by the Food and Drug Administration and by the Johns Hopkins Internal Review Board, and a clinical study has just started. Urologists including Mohamad Allaf and Ashley Ross perform the biopsies. “To the best of our knowledge, this is the only robot approved by the FDA to operate in the MR environment in general, not only for the prostate,” says Stoianovici. “The first clinical cases suggest that robotic biopsy is safe and feasible.”

With more precise knowledge of suspicious areas to investigate, urologists may be able to make biopsies even more accurate at determining the true picture of cancer within the prostate. This technology may also help radiation oncologists achieve more precise implantation of radiation seeds in brachytherapy. Stoianovici presented this work at the annual meeting of the American Urological Association, where it was awarded Best Paper of the Engineering and Urology Society. Other authors of the paper include Chunwoo Kim, Changhan Jun, Doru Petrisor, Katarzyna Macura, Ross, and Allaf. ■



Edward Schaeffer and Chris Evensen: One of our finest clinician-scientists is the first recipient of the Professorship named after one of the Brady's greatest friends.

“Chris Evensen has been selfless in his support of our research. He treats this as his full-time job and his impact has been incredible.”

Schaeffer Named Inaugural Evensen Professor

R. Christian B. Evensen doesn't have prostate cancer anymore, and many men in his shoes would prefer never to think about the prostate again. Instead, Evensen has become one of the best friends the Brady Urological Institute has ever had and has given his time, talent, and treasure to erase this disease from the face of the earth. He is one of the charter founders of the Patrick C. Walsh Prostate Cancer Research Fund; has served as the Chair of the Johns Hopkins Prostate Cancer Advisory Board for many years; has been as a lay member on the committee that awards the Patrick C. Walsh Prostate Cancer Research Scholarships; and now, he has endowed a professorship.

“What Chris has done is remarkable,” says Patrick Walsh, M.D., University Distinguished Service Professor of Urology. “He has been selfless in his support of our research, traveling across the country from Los Angeles to meet and mentor investigators at 6 a.m. before attending long board meetings. A week does not go by when I do not receive an e-mail asking about the importance of some new research finding or suggesting another way that he can help. He treats this as his full-time job and his impact has been incredible. And now he has honored one of our finest clinicians and scientists with a Professorship that bears his name.”

The inaugural recipient of the R. Christian B. Evensen Professorship, dedicated in June, is Edward M. Schaeffer, M.D., Ph.D., associate professor of Urology and Oncology. “I am honored to be the R. Christian B. Evensen Professor,” says Schaeffer, “and I am inspired by the confidence that Chris Evensen has shown in the work we are doing.”

Schaeffer, who directs the Brady's Prostate Cancer Program, is also Co-Director of the Prostate Cancer Multidisciplinary Clinic and Director of International Urologic Services. “Ted Schaeffer exemplifies the mission of the Brady Urological Institute by seamlessly combining surgical acumen and scientific discovery,” says Walsh, who recruited Schaeffer as a resident to the Brady 13 years ago. “The central theme of his research involves understanding the clinical, biologic and molecular features of the most aggressive types of prostate cancer.” Schaeffer's work is supported by the NIH, the Howard Hughes Institute, the Department of Defense, and the Prostate Cancer Foundation.

In laboratory work, Schaeffer has developed several novel approaches to finding how prostate cancer starts at the molecular level. He is particularly interested in understanding the basic processes that determine and drive aggressive prostate cancer, and in

helping the men at highest risk of developing this most dangerous form of the disease. His most recent work (see next page) on disparities in outcomes for African Americans with prostate cancer was honored by the American Society of Clinical Oncology with a 2013 Clinical Cancer Advance award. Schaeffer has also been awarded the American Urological Association's Astellas “Rising Star” award and the Howard Hughes Clinician-Scientist Early Careers Award. He has written more than 120 peer-reviewed papers and has edited and contributed to multiple medical textbooks.

Evensen is the Founding and Managing Partner of Flintridge Capital Investments, an algorithmic trading firm, and Flintridge Capital Technologists, which develops these technologies. He is a Trustee of Johns Hopkins Medicine, where he is a member of the Finance Committee and Investments Subcommittee; a board member of Johns Hopkins Medicine International; and also a board member of the Prostate Cancer Foundation, where he is the Chair of the Discovery and Translation Committee and the Development Committee; and a board member of the Prostate Cancer Foundation of Norway. He and his wife, Felicia Evensen, have six children. ■

For African American Men, Early Detection of Prostate Cancer is Crucial

Scientists have known for years that prostate cancer is worse in African American men. New research by urologist Edward Schaeffer, M.D., Ph.D., the R. Christian B. Evensen Professor (see previous story) helps explain why this happens, why black men should be extra vigilant in getting checked for prostate cancer and why, if cancer is found, they should seek curative treatment.

In a recent study, accepted for publication in the journal, *Urology*, Schaeffer looked at the outcomes of more than 17,000 men who underwent radical prostatectomy at Johns Hopkins. Of these men, 1,650 were African American, and many of them “were more likely to have higher-grade cancer at the time of surgery than the original biopsy had determined,” says Schaeffer. “They were more likely to have the cancer pushing outside of the prostate, as well. We also found that African American men were more likely to experience recurrence compared to Caucasian men with the same grade and stage of cancer.”

For example: Compared to Caucasian men with clinical stage T1c disease, African American men “had higher post-prostatectomy Gleason scores, greater cancer volume, and greater tumor volume in their serum PSA,” Schaeffer says. This finding is consistent with other research that suggests that in African American men, prostate cancer grows and progresses more rapidly than it does in other men, with four-fold higher rates of metastatic disease.

Although racial disparities in the incidence and outcomes of prostate cancer likely have many causes, “biologic differences seem to be key contributing factors,” Schaeffer notes. “These results suggest that African American men need heightened awareness about prostate cancer. Our African American patients need to know that they are likely to harbor

more aggressive disease than the biopsy suggests, and that their prostate cancer may be more aggressive than prostate cancer in other men.”

“Our African American patients need to know that they are likely to harbor more aggressive disease than the biopsy suggests, and that their prostate cancer may be more aggressive than prostate cancer in other men.”

The take-home message, Schaeffer says, is that “African American men really need to know their stats. If there is a change in their PSA or exam, we recommend a biopsy. If the biopsy shows cancer, we advocate expedient aggressive treatment. With these actions, African American men with prostate cancer are still curable.”

Co-contributors to this paper are Farzana Faisal, a Hopkins medical student and first author, and urology resident Deb Sundi, M.D. ■

Target: Hedgehog Pathway

New Trial Opens for Men with High-Risk Prostate Cancer

Why are urologists getting excited about a pathway named after a hedgehog? Because this critical signaling pathway (discovered in mice with prostate cancer in 2005 by Hopkins scientists David Berman and Philip Beachy) is known to be important for the growth and spread of prostate cancer. And, says urologist Ashley Ross, M.D. Ph.D., Assistant Professor in Urology, Oncology, and Pathology, because men with high-risk prostate cancer are badly in need of a drug that could potentially prevent cancer growth and metastasis by targeting this pathway. “By looking at gene expression patterns, we and others have found that the Hedgehog

pathway appears up-regulated in men with disease that metastasizes after local therapy. Also, in men with advanced prostate cancer, Itraconazole, which inhibits the Hedgehog pathway, appears to slow the disease by a mechanism independent of the androgen receptor. Itraconazole is an antifungal drug. Recently, new, Hedgehog pathway-specific drugs with much more favorable toxicity profiles are available.”

Ross, with oncologist Emmanuel Antonarakis, is beginning a randomized, placebo-controlled clinical trial of a highly selective Hedgehog pathway inhibitor, called LDE225 and made by Novartis. “The men who receive the drug will take it orally in pill form for four weeks.” Men will begin taking the inhibitor about a month before radical prostatectomy. All of the men will undergo a repeat biopsy and will have a molecular profile done on their cancer cells before surgery, and then will have the radical prostatectomy specimens examined afterward. “It’s a pharmacodynamic trial, to see if this new drug actually gets into the prostate and inhibits the Hedgehog pathway as we expect it should. Of course, men will be followed closely following prostatectomy and we will also monitor whether superior cancer control results are achieved in those who received LDE225.”

The trial is open to radical prostatectomy patients at Johns Hopkins with high-risk prostate cancer: men with a Gleason score of 8 to 10, a PSA of 20 or greater, or clinical stage T3 disease. In patients who have high-risk prostate cancer, there is always the possibility that, even after surgery or radiation therapy, some cancer cells have already escaped the prostate, are hiding somewhere in the body, and will repopulate. Use of a systemic Hedgehog inhibitor may help wipe out these “micro-metastatic” cells.

“We need to start thinking of high-risk disease as a different type of cancer,” says Ross, “a systemic disease, and we have to start treating them like we treat other cancers, with a systemic approach in addition to surgery and/or radiation.” ■

Two Genetic Warning Signs for Potentially Lethal Prostate Cancer

Like tumbleweeds, prostate cancers can pick things up as they move along. In this case, the debris they acquire is genetic. “Prostate cancers accumulate genetic alterations of many types,” says molecular geneticist William Isaacs, Ph.D. Some of these are fairly simple changes, where one or a few DNA bases are substituted for the normal sequences. Then there are bigger changes called “copy number alterations,” where much larger sequences of DNA are gained or deleted. “It’s not uncommon for large pieces of chromosomes, each containing genes important in regulating tumor growth, to be gained or discarded from the genome of cancer cells,” he adds.

Men who had both of these genetic changes were 10 to 50 times more likely to die from prostate cancer than men who had neither.

Could these copy number alterations be of significance? Isaacs, the William Thomas Gerrard, Mario Anthony Duhon and Jennifer and John Chalsty Professor of Urology and Professor of Oncology, recently took a closer look at these jumbo alterations, and found that the answer was a definite “yes.”

“Together with our colleagues at the Karolinska Institute in Sweden and Wake Forest University, we searched each chromosome for copy number variants that might tell us which prostate cancers are more likely to progress to lethal disease.” In their initial analysis of 125 men with long-term followup after undergoing radical surgery at Johns Hopkins, they identified 20 chromosomal regions that show a tendency to be gained or lost in the cancer cells, compared to normal cells in these men.

What they found was striking: “Of these regions, seven were more com-

mon in men who went on to develop lethal prostate cancer,” says Isaacs. The two regions that were the most significant in predicting which men would die from prostate cancer were located on chromosomes 8 and 10, and contained two familiar genes, MYC and PTEN, respectively – both known to play important roles in the formation of prostate cancer. Men whose tumors had both of these changes, the loss of PTEN at 10q21 and the gain of additional copies of MYC at 8q24, “were 10 to 50 times more likely to die from their disease than patients whose tumor cells maintained normal copy numbers of these genes.”

Next, the scientists confirmed these associations in an analysis of over 300 additional patients from the U.S. and Sweden. “This study strongly suggests that measurement of tumor cell copy number of PTEN and MYC can be used to identify men at substantially increased risk of dying of their prostate cancer who need more aggressive treatment.” Isaacs notes that this work independently confirms the work of Hopkins scientists Tamara Lotan and Angelo De Marzo, “who have come to a similar conclusion regarding the ability of PTEN gene loss to predict poor outcome in men undergoing a radical prostatectomy for clinically localized prostate cancer.” This work was published in *Cancer*.

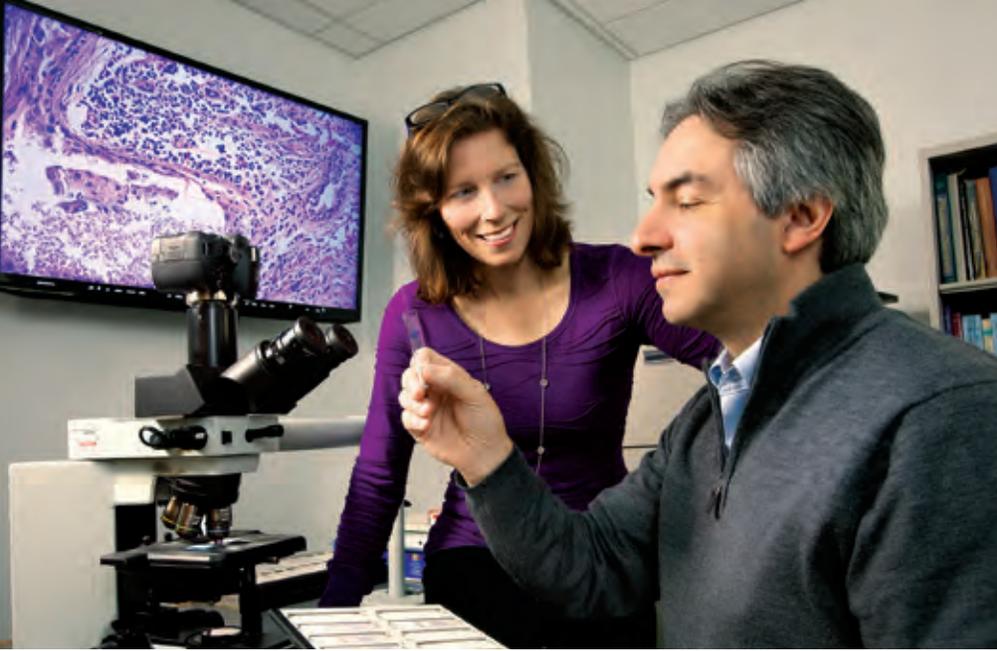
The Gleason Score as Crystal Ball

In last year’s *Discovery*, we featured the research finding by pathologist Jonathan Epstein, M.D., the Reinhard Professor of Urologic Pathology, that when Gleason 6 cancer is found at radical prostatectomy, the cancer never spreads to the pelvic lymph nodes. In a recent study, published in the *British Journal of Urology*, Epstein and colleagues further demonstrated what he calls the “good behavior” of Gleason 6 cancer. “Even when there are multiple cores of Gleason grade 6 on a

biopsy, the prognosis is still favorable,” he says. For example, “even with more than 6 cores containing Gleason score 6 cancer, 84 percent of men will be cured with surgery.” With a low PSA (less than 4 ng/ml), despite having four to six positive cores, the tumor will still be confined to the prostate in more than 75 percent of men. “The good news is that low-grade cancer trumps more extensive tumor on biopsy.”

“The good news is that low-grade cancer trumps more extensive tumor on biopsy... and even with the worst Gleason grade, there are some men with limited disease who do well and can be cured by surgery.”

Epstein and colleagues also explored the significance of cancer at the other, most aggressive end of the Gleason spectrum, Gleason 9 and 10 tumors. This work was published in the *Journal of Urology*. “For the relatively few men with low-volume Gleason 9 cancer, limited to one core, there is a good chance that the tumor will be organ-confined at radical prostatectomy,” Epstein reports. “However, in most men with more extensive Gleason 9-10 cancer on biopsy, fewer than one out of five men will have tumor confined to the prostate.” These two studies show why the Gleason score remains such a powerful barometer indicating the aggressiveness of prostate cancer. However, Epstein notes, “even with the worst Gleason grade, there are some men with limited disease who do well and can be cured by surgery.” ■



Platz and De Marzo: Inflammation is a warning sign that potentially lethal cancer may be present.

Cancer is More Likely When There's Inflammation in Normal Prostate Tissue

Why is the prostate prone to chronic inflammation, and what role, if any, does this inflammation play in the development of prostate cancer? These are questions that epidemiologist Elizabeth Platz, Sc.D., M.P.H., and pathologist Angelo De Marzo, M.D., Ph.D., have been investigating for 15 years, and in their latest research, they have found that men who have inflammation in normal prostate tissue may be nearly twice as likely to have cancer, and to have cancer of a higher grade.

This research doesn't prove that inflammation actually causes prostate cancer, but it is a warning sign that potentially lethal cancer might be present — and it also represents an exciting potential avenue for preventing the disease.

For years, De Marzo, Professor of Pathology, Oncology, and Urology, has seen inflammatory cells in prostate biopsies, radical prostatectomy specimens, and in tissue resected for treatment of BPH (benign enlargement of the prostate). “There are infections and diseases associated with inflammation in liver, stomach, and colon cancers,” he says, “and it is possible that inflammation could serve as an initiator and/or promotor of prostate cancer, as well.”

In a recent study, published in *Cancer Epidemiology, Biomarkers, and Prevention*, Platz and De Marzo investigated the connection between inflammation and

prostate cancer. “We wanted to make sure that there was no potential for bias,” says Platz, Professor of Epidemiology, Oncology, and Urology. In the U.S. and other countries where PSA testing is routine, it is possible that the men who get prostate biopsies do so because inflammation has caused their regularly tested PSA to go up. “Prostate cancer is more likely to be detected in these men; thus, we chose to look for cancer in men who had no apparent cause to undergo a biopsy.”

In this study, De Marzo and Platz studied men in a setting where this bias would be less likely: SWOG's Prostate Cancer Prevention Trial. “The men who were not diagnosed with prostate cancer during this trial were recommended to have a prostate biopsy at the end, even if they had a normal PSA and digital rectal examination,” says Platz. “This meant that we had access to prostate tissue from men who had no suspicious signs that cancer might be present.”

The study included 191 men with prostate cancer that had been detected by biopsy, and 209 matched controls. Bora Gurel, M.D., a pathology fellow at the time of the work and the paper's first author, looked for inflammation in benign tissue in the biopsy cores. He recorded the presence of any inflammatory cells and determined the proportion of the total benign biopsy core area that showed any inflammatory cells.

“It turned out that chronic inflammation was very common within the prostate,” says De Marzo. The scientists found inflammation in about 86 percent of the men with prostate cancer, but also in about 78 percent of the men who had not been diagnosed with cancer. “Men who had inflammation in at least one biopsy core had higher odds of having prostate cancer, and even higher odds of having higher-grade prostate cancer (Gleason 7-10).” Even in men with low PSA levels (less than 2 ng/ml), this association between inflammation and both total and higher-grade prostate cancer remained.

“Men who had inflammation in at least one biopsy core had higher odds of having prostate cancer, and even higher odds of having higher-grade prostate cancer.”

In related news: In 2014, Platz was named a Mentor of Excellence by the Prostate Cancer Foundation, and she also received a Teaching Award from the Brady Urological Institute. ■

Not All High-Risk Prostate Cancer is Equal

When a man is diagnosed with prostate cancer, doctors look at his PSA level, clinical stage, and the Gleason score of the biopsy tissue samples to assign that cancer a risk factor. “Knowing whether it’s low, intermediate, or high-risk prostate cancer can help patients and their physicians determine roughly how aggressive the cancer is,” says Trinity Bivalacqua, M.D., Ph.D., “and that, in turn, helps determine the best course of treatment.” However, new research done by Bivalacqua, Debasish Sundi, M.D., and colleagues suggests that not all high-risk prostate cancer is the same. This work was published in the May 2014 issue of the journal, *Prostate*.

“Some men with high-risk disease are cured with treatment such as radical prostatectomy, while other men in the same high-risk category, even after undergoing aggressive treatment, will experience a rapid recurrence of their cancer,” says Bivalacqua, Director of Urologic Oncology, and “this issue can present a dilemma to patients and their urologists trying to formulate an optimal treatment plan.”

With the hope of fine-tuning the high-risk category and predicting which men have the most aggressive cancer, Sundi and Bivalacqua designed a study of men with high-risk prostate cancer who underwent radical prostatectomy. “We wondered if we could determine which ones are most likely to experience early cancer recurrence,” says Sundi. (Early recurrence is defined in this study as having a detectable PSA of 0.2 ng/ml or greater within the first year after treatment.) “We needed to use precise pre-treatment predictors,” Bivalacqua explains, “because by the time pathologic data are available, the men with the most aggressive cancers may potentially have missed their window to try a more intense, multimodal treatment approach.”

Sundi, Chief Resident of Urology and lead author on the paper, says, “we found that men meeting a certain set of criteria were the most likely to

experience early biochemical recurrence. Furthermore, these same men were at a more than threefold higher risk of having the cancer spread to distant sites, and dying from their cancer,” than other high-risk men. Clearly, says Bivalacqua, “there are significant differences even within this single group of ‘high-risk.’” Men at highest risk of early recurrence of cancer were found to have either primary Gleason pattern 5 present on any biopsy core; or four or more biopsy cores containing Gleason pattern 4, primary or secondary. (In a Gleason score such as 3+4, the primary pattern is the first number, 3, and the secondary pattern is the second number, 4.)

“The fact there is such variation in the clinical outcomes of men with high-risk prostate cancer suggests that we should not treat everyone the same.”

“The fact there is such variation in the clinical outcomes of men with high-risk prostate cancer suggests that we should not treat everyone the same,” Bivalacqua adds. This study suggests that “high-risk men who meet early-recurrence criteria, whom we would predict to have much more aggressive cancers, should be offered more aggressive treatments up front.” For example, to maximize their chances of cure, these men might strongly consider enrolling in a clinical trial of neoadjuvant therapy before surgery. “Patients should be aware of precisely how aggressive their prostate cancer might be. It affects the optimal treatment strategy, which might involve a multidisciplinary approach.” ■

One Small Gene May Answer Big Question: Will My Cancer Come Back?

If you’ve been diagnosed with prostate cancer, the question you most want answered may be, “Do we need to treat this, or can we just watch it?” If you’ve already been treated with surgery, the question is most likely, “Is the cancer gone, or will it come back?”

“Thankfully, there are a few useful indicators that can help answer these questions, such as the Gleason grade of the biopsy or surgical specimens,” says Shawn Lupold, Ph.D., Associate Professor of Urology and Oncology. But better predictors are sorely needed, he says.

Lupold has been studying a promising new class of genes, called microRNAs, to determine if they play a role in the development and progression of prostate cancer. Recently, with a team of researchers from the Bloomberg School of Public Health and the Department of Pathology, he analyzed the potential of some of these microRNAs to be markers of risk for the recurrence of prostate cancer after surgery. “For this study, we were fortunate to have access to a very valuable set of radical prostatectomy tissue specimens,” developed by epidemiologist Elizabeth Platz, Sc.D., M.P.H., and pathologist Angelo De Marzo, M.D., Ph.D.

They found that in the tumors that recurred, there was a significantly lower level of one microRNA, miR-221.

In this case-controlled study, the scientists looked at 118 tumors from radical prostatectomies performed between the years of 1993 to 2001; half of the tumors recurred after surgery. The tumors where cancer came back were carefully matched with tumors where cancer did not recur by factors including age, race, pathologic stage, and Gleason grade, “with the hope that

new and different markers associated with recurrence could be discovered,” Lupold explains. They found that in the tumors that recurred, there was a significantly lower level of one microRNA, miR-221. “These results are promising and they shed new light on miR-221 expression as a potential mechanism for cancer progression,” Lupold says. He notes that larger studies are needed to validate these results and to figure out how best to use this biomarker as a measure of risk.

Also promising for the future, says Lupold, is that “this work is an excellent example of the collaborative nature of the prostate cancer research group at Johns Hopkins. The open discussions and working relationships among molecular and cell biologists, geneticists, pathologists, surgeons, epidemiologists, patients and biostatisticians led to the development of this valuable case-control study set, which has been used to evaluate several new biomarkers over the last five years.” Every month, Lupold meets with an interdisciplinary group of scientists including Platz, De Marzo, Corinne Joshi, Christopher Heaphy, and Alan Meeker. “Over coffee, we review laboratory results, discuss ideas, and develop new collaborative projects in the prostate cancer research field,” he says. Two emerging projects from this collaboration include studying the role of microRNAs in cancer that has become resistant to hormonal therapy, and cancer that resists radiation therapy.

This work was recently published in *The Prostate*. ■

Should We Rethink Gleason Pattern 3 Cancer?

It’s not “CSI,” but the same forensic autopsy approach that helps police capture a murderer has shed new light on the prostate cancer that proved lethal for a man who died 17 years after diagnosis, and the results have stunned Hopkins scientists.

When “John” died of high-grade, advanced prostate cancer, Hopkins pathologists performed an autopsy. Using highly sophisticated, whole-genome sequencing analysis, they were able to characterize multiple, distinct lesions of cancer. They were also able to compare the cancer obtained at the autopsy with earlier samples from a biopsy of a metastatic lesion taken a few years before his death, and even earlier, from John’s radical prostatectomy specimen.

What they did was akin to tracing cancer, through its distinctive fingerprints, back in time. What they found has never been shown before.

What they did was akin to tracing cancer, through its distinctive fingerprints, back in time. What they found has never been shown before. “Molecular genome analysis revealed that 85 coding mutations and 226 structural rearrangements were shared by each of the metastatic lesions, indicating that the progeny of a single clone were responsible for the spread of lethal cancer,” says William Nelson, M.D., Ph.D., the Marion I. Knott Professor of Oncology and Director of the Sidney Kimmel Comprehensive Cancer Center.

Here’s the stunning part: That cancer was Gleason pattern 3. “This Gleason pattern 3 was in the radical prostatectomy specimen,” says Nelson. Although the predominant cancer in the tumor was Gleason pattern 4, the two types of cells did not share the same

characteristics. “The Gleason pattern 3 disease had some high-risk features, including a p53 mutation and PTEN loss (covered in previous issues of *Discovery*; please see our website), that are otherwise rare in primary prostate cancer. They are rarer still in Gleason pattern 3 prostate cancer.” Those high-risk characteristics allowed John’s cancer to defy several treatments, including radical prostatectomy, vaccine immunotherapy, hormonal therapy, chemotherapy, and radiation therapy.

The fact that a pattern of cancer that is considered to be “good” can be lethal may mean scientists need to rethink Gleason pattern 3 — or at least, to stratify it based on whether these high-risk features are present — and that certain men with Gleason pattern 3 disease might need early, aggressive treatment. “The findings represent an interesting use of autopsy for lethal prostate cancer in a ‘forensic’ mode,” says Nelson, tracking its evolution “with the hope of ascertaining how cancer progresses despite available treatment, and discovering new ways to prevent prostate cancer deaths.”

This work was published in the *Journal of Clinical Investigation*. The study’s authors, besides Nelson, include Michael Haffner, Timothy Mosbrugger, David Esopi, Helen Fedor, Christopher Heaphy, DA Walker, Nkosi Adejola, Bora Gurel, J. Hicks, Alan Meeker, Marc Halushka, Jonathan Simons, William Isaacs, Angelo De Marzo, and Srinivasan Yegnasubramanian. ■



Partin and Epstein: Test predicts whether cancer may have been missed on the biopsy.

If the biopsy needles can't always find cancer, is it possible that the presence of these other somewhat weird, hypermethylated cells might act as the proverbial canary in the coal mine? A new test suggests that the answer is yes.

New Test May Help Avoid Repeat Biopsies

Nearly one million American men undergo a prostate biopsy every year. Three out of four of these men will be told that they don't have cancer because when pathologists looked at their tissue cores under the microscope, they didn't see anything suspicious. However, of these 750,000 negative biopsies, an estimated one-fourth — nearly 190,000 men — actually do have prostate cancer; the biopsy needles just missed it. Many of these men will have to go through at least one repeat biopsy, maybe more, before their cancer is diagnosed.

For more than 20 years, ever since regular screening for prostate cancer began to be widespread, doctors have looked for a way to avoid unnecessary repeat biopsies. At the same time, Brady scientists led by William Nelson have been studying the nature of prostate cancer cells, and of the cells percolating alongside the cancer. They noticed that many of these cells showed methylation changes — “epigenetic” changes to the biochemical composition of their DNA that make the cells act differently.

If the biopsy needles can't always find cancer, is it possible that the presence

of these other somewhat weird, hypermethylated cells might act as the proverbial canary in the coal mine? A new test, a tissue assay called Confirm MDx, suggests that the answer is yes.

“This assay looks at the methylation, the alteration of the DNA, of three genes,” says Alan W. Partin, M.D., Ph.D., the David Hall McConnell Professor and Director of the Brady, “and predicts whether cancer may have been missed and that a repeat biopsy should be recommended.”

Recently, Partin and pathologist Jonathan Epstein, M.D., led a multicenter study of 350 men who had undergone PSA tests and who had high-risk variables (such as high-grade PIN and a high PSA), but who had a negative prostate biopsy. The men were patients at five major urologic centers, including Hopkins; the study was called DOCUMENT, for Detection of Cancer Using Methylated Events in Negative Tissue. The tissue methylation assay was used to analyze the DNA from 3,687 negative tissue cores for epigenetic abnormalities, and the results were compared to findings on a repeat biopsy done within two years. Epstein, the

Reinhard Professor of Urologic Pathology and Director of Surgical Pathology, reviewed all of the biopsy tissues.

The assay performed like a champ, accurately ruling out the presence of cancer up to 88 percent of the time. The study's results were published in the *Journal of Urology*. “This study shows that by looking for the presence or absence of cancer in a different way, we may be able to offer many men peace of mind without putting them through the pain, bleeding, and risk of infection that can come with a repeat biopsy,” says Epstein. “With prostate biopsies, there is often very little cancer, which makes it difficult to perform molecular prognostic and predictive tests. The DOCUMENT study overcomes this problem, because it looks at benign tissue, not just the cancer. There is a lot of benign tissue, which is why we think it performs so well.

“Overall, if there is an absence of methylation in all three biomarkers, there is an 88 percent likelihood you don't have cancer,” Epstein says. “The test isn't 100 percent perfect, but it is a major step forward.” ■

Good news for men with asthma:

Asthma and Prostate Cancer

You have a lower risk of prostate cancer, especially the most lethal kind! You may also take comfort in knowing that you have surprised some of Hopkins' finest investigators.

Scientists have long believed that chronic inflammation of the prostate gland is associated with the development of prostate cancer (for some of the latest exciting work on this, see story on Page 11). However, the nature of that inflammation is not well-understood. Charles Drake, M.D., Ph.D., Associate Professor of Oncology, Immunology, and Urology, and Co-Director of the Prostate Cancer Multi-Disciplinary Clinic, explains: "This is important because if we could understand the precise immunological mechanisms by which inflammation can promote prostate cancer, it could lead to the development of treatments that dampen chronic prostatic inflammation, or even prevent that inflammation from promoting cancer development."

Several laboratory studies supported the idea that chronic inflammation that leads to cancer is driven by the presence of a certain family of inflammatory molecules, or cytokines. This family is called the TH2 family, and "interestingly, that same family of cytokines has been shown to be involved in a very common chronic inflammatory condition — asthma," says Drake. So, Drake hypothesized that men with a history of asthma

would have a tendency to develop chronic TH2-mediated inflammation, and would be thus at a greater risk for prostate cancer. Working with colleagues from Harvard, Drake and Elizabeth Platz, Sc.D., M.P.H., Professor of Epidemiology, Oncology, and Urology, tested that hypothesis in 47,880 men participating in the Health Professionals Follow-up Study. These men were free of the diagnosis of prostate cancer when they enrolled in 1986; just over 9 percent of them had asthma. By 2012, 6,294 of the men were diagnosed with prostate cancer, and of these, 798 were metastatic at diagnosis or during follow-up, or fatal.

"It turned out that men with asthma had a lower risk of prostate cancer, especially lethal prostate cancer."

Surprisingly, they found "the exact opposite result" of the study's hypothesis," Drake says. "It turned out that men with asthma had a lower risk of prostate cancer, especially lethal prostate cancer. The association was strongest for fatal prostate cancer; men with asthma had a 36 percent lower risk."

This surprising result has profound implications for the idea that TH2 inflammation is a contributor to cancer in humans. "One possibility is that the kind of inflammation that drives prostate cancer development is of another sort, possibly TH17 inflammation, which involves very different cytokines," says Drake. It's also possible that if the immune system is focused on promoting inflammation in one site, such as the lung, then cancer-promoting inflammation in other sites could be less likely to occur. Finally, "it's also possible that the mice have been leading us astray, and that TH2-mediated inflammation is not the kind of inflammation that leads to cancer in humans." Drake plans further work in collaboration with pathologist Angelo De Marzo to test for the presence of TH2 inflammation in actual tissue samples. "These findings

are the fruit of a productive collaboration of basic immunology, epidemiology and pathology, and represent the kind of team science that will be important in finding new ways to treat or even prevent prostate cancer." ■

Salvage Radiation Therapy and Enzalutamide: A Winning Combination?

The vast majority of the estimated 30,000 American men who will die of prostate cancer this year originally were treated for localized prostate cancer with radical prostatectomy or radiation, but the cancer came back and spread. "When the PSA initially comes back after surgery, this is the time when these men are still potentially curable with salvage radiation," says Phuoc T. Tran, M.D., Ph.D., Associate Professor of Radiation Oncology and Molecular Radiation Sciences, Oncology and Urology.

The window of curability is still open for these men, Tran says, and he wants to maximize their chances of cure. "Salvage radiotherapy is the mainstay of treatment for men with a persistently detectable PSA or a delayed rise in PSA without evidence of metastasis," he notes. "But it is clear that salvage radiotherapy alone is not likely to guarantee freedom from PSA progression or cure in most high-risk men." Tran hopes that adding drugs that target the androgen, or male hormone, receptors to salvage radiation therapy will prove to be the winning combination to knocking out the cancer while it is still curable.

Androgen receptor-blocking drugs impair growth in the majority of prostate cancers, and androgen deprivation (hormonal therapy) drugs also kill many prostate cancer cells; however, "those cells that do not die will ultimately become resistant and will grow despite

Continued on page 16 »



Drake: Good news for men with asthma.

Continued from page 15 »

androgen deprivation,” says Tran. Several randomized trials have shown that hormonal therapy improves overall survival in men who are receiving primary radiation therapy for prostate cancer. “But there is no consensus on how to apply androgen deprivation, or which patients undergoing salvage radiotherapy would benefit most.” The drug bicalutamide, a first-generation androgen receptor blocker, has been used successfully in combination with salvage radiation therapy.

But enzalutamide, a second-generation androgen receptor blocker, looks even more promising, Tran says. “Enzalutamide significantly prolongs survival in patients with metastatic, castration-resistant prostate cancer given either before docetaxel chemotherapy or even after.” Enzalutamide is taken orally and is generally well tolerated, “which makes it an ideal candidate for combination with salvage radiotherapy. Also, provocative preliminary Phase II data presented at the American Society of Clinical Oncology’s annual meeting in 2013” by medical oncologists at Massachusetts General Hospital “assessed the efficacy and safety of six months of enzalutamide alone in men with prostate cancer of all stages who had never received hormonal therapy.

Enzalutamide alone for six months achieved a high PSA response rate, but in contrast to hormonal therapy had much fewer side effects.”

“Our hope with this trial is to improve outcomes in high-risk men with biochemical failure following radical prostatectomy, and to significantly reduce the number of men who die of prostate cancer each year.”

Tran and medical oncologist Emmanuel Antonarakis will soon be launching a multicenter, randomized Phase II clinical study of salvage radiation therapy with or without enzalutamide in men who have a detectable or rising PSA after radical prostatectomy. “This trial will allow us to determine the efficacy of adding a second-generation androgen receptor blocker with salvage radiation therapy,” says Tran. “Our hope with this trial is to improve outcomes in high-risk men with biochemical failure following radical prostatectomy, and to significantly reduce the number of men who die of prostate cancer each year.” ■



Chan: Outstanding work in clinical chemistry.

Chan Wins Award

Daniel W. Chan, Ph.D., Professor of Pathology, Oncology, Urology, and Radiology, has been honored with the American Association for Clinical Chemistry’s Miriam Reiner Award for his outstanding contributions to research in clinical chemistry.

Chan, an internationally recognized expert in immunoassay, clinical proteomics, and biochemical tumor markets, has edited and written five books on immunoassay, immunoassay automation, diagnostic endocrinology, and tumor markers, and has published more than 200 articles. ■

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“New Era” in Treating Metastatic Kidney Cancer

Results of two important studies bring good news to those who suffer from metastatic kidney cancer. “A new class of drugs is changing our approach to kidney cancer: the immune checkpoint inhibitors,” says Hans-Joerg Hammers, M.D., Ph.D.

When Cancer Extends Beyond the Prostate

At radical prostatectomy, some men are found to have cancer that extends

slightly beyond the prostate. A new study shows that for the vast majority of men, this does not increase the risk of dying from prostate cancer, says urologist Misop Han, M.D.

New Imaging System Makes Brachytherapy More Accurate

Danny Song, M.D., Junghoon Lee, Ph.D., and Hopkins colleagues have developed a system that allows precise visualization of seeds during brachytherapy. This system links an x-ray machine to an ultrasound.

Looking to Identify High-Risk Men Early

Some low-risk cancers may harbor very subtle features of an aggressive cancer, says Robert Veltri, Ph.D., “If these men could be identified early, we could eradicate their cancer when the disease burden is low.” He and colleagues have identified a promising biomarker that may lead to an early test.

Read About the Research You have Helped Make Possible.

THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND

Since its inception in 2005, the Patrick C. Walsh Prostate Cancer Research Fund has awarded millions of dollars to Johns Hopkins scientists in every discipline with good ideas worth pursuing that can help us understand more about prostate cancer — and ultimately, help us find the cure. Applications are reviewed by a Scientific Advisory Board composed of noted Hopkins scientists. These awards wouldn't have been possible without the tremendous and amazing generosity of our patients and friends. On these pages you'll find some of the exciting work this year's award winners are doing, and the work of Jun Luo, the R. Christian B. Evensen Scholar, is featured on Page 3.

2014 AWARDEES

Angelo De Marzo, M.D., *The Virginia and Warren Schwerin Scholar*

Theodore L. DeWeese, M.D., *The Peter Jay Sharp Foundation Scholar*

Christopher Heaphy, Ph.D., *The Dr. and Mrs. Peter S. Bing Scholar*

Paula Hurley, Ph.D., *The Beth W. and A. Ross Myers Scholar*

Jun Luo, Ph.D., *The R. Christian B. Evensen Scholar*

Ben Ho Park, Ph.D., *The Irene and Bernard L. Schwartz Scholar*

Venu Raman, Ph.D., *The Carolyn and Bill Stutt Scholar*

Scott Zeger, Ph.D., *The Nancy and Jim O'Neal Scholar*

A Better Way to Detect Epigenetic Changes

There are genetic changes in cancer — changes in the DNA sequence of genes that spark unbridled cell growth and replication and lead to cancer — and then there are “epigenetic” changes. These are changes that can turn off or turn on a gene without changing the DNA sequence. This can happen in cancer cells and also in precancerous cells; currently, these changes are not very easy to detect and monitor. “Most of the ways we can determine the presence of epigenetic changes involve averaging signals from assays that are designed to look for changes in many cancer cells,” says Angelo M. De Marzo, M.D., Ph.D., Professor of Pathology, Oncology, and Urology. “However, these techniques can't determine, at the single cell level, precisely which changes are occurring in which cell types. This limits our understanding of how cancers arise and progress.”

For example, some epigenetic changes involve subtle changes of DNA methylation — basically, these changes are akin to fiddling with the tumblers on a lock. “DNA methylation alterations in prostate cancer have been shown to have extremely high sensitivity and specificity for distinguishing prostate cancer tissues from normal tissues,” but to spot them, scientists must extract DNA from cells and then subject it to various solution-based assays, a process that is time-consuming and expensive.

A great deal of the work showing extensive, prostate cancer-specific DNA methylation alterations has been conducted by Srinivasan Yegnasubramanian, M.D., Ph.D., Associate Professor of Oncology. Yegnasubramanian first started on DNA methylation studies in prostate cancer when he worked in the laboratory of William G. Nelson, M.D., Ph.D., as a graduate student, and he has continued this work as an independent investigator.

Wouldn't it be nice if scientists could measure these changes right in the specimens of prostate tissue? De Marzo and a team of investigators, who have worked together on DNA methylation changes in prostate cancer for more than a decade, are determined to overcome this roadblock. The fact that there isn't a good way to do this kind of “*in situ*” testing, they realized, has prevented pathologists from routinely checking for methylation changes to help diagnose prostate cancer, and it's prevented scientists from using it to study prostate cancer. “Clearly, the development of next-generation technologies for *in situ* detection of epigenetic changes would be of immense value in improving our understanding and clinical management of prostate and other cancers.”

Wouldn't it be nice if scientists could measure these subtle changes right in the prostate tissue?

With support from the Patrick C. Walsh Prostate Cancer Research Fund, De Marzo, the Virginia and Warren Schwerin Scholar, Yegnasubramanian, Nelson and post docs Michael Haffner, M.D. Ph.D., and Ibrahim Kulac, M.D., are working to develop such highly innovative technologies to enable the detection of epigenetic changes *in situ*, “with a high degree of sensitivity down to single-molecule detection.” ■

Read About the Research You have Helped Make Possible.

A New Way to Track Prostate Cancer's Response to Treatment

Is the treatment killing the cancer? This is a question that Theodore L. DeWeese, M.D., Director of Radiation Oncology and Molecular Radiation Science, oncologist Srinivasan Yegnasubramanian, M.D., Ph.D., and postdoctoral fellow Omar Mian would really like to be able to answer in as little time as possible, because with high-risk prostate cancer, the stakes are high.

This year, nearly 30,000 American men are estimated to die of prostate cancer, says DeWeese, the Peter Jay Sharp Foundation Scholar. “Many of these men were initially diagnosed with aggressive, or high-risk prostate cancer,” perhaps with disease that extended beyond the prostate, or had a high Gleason score, or a PSA level greater than 20 ng/ml. “Nearly half of these men will have a recurrence of their cancer after treatment.”

A mainstay of care for men with high-risk prostate cancer is a combination of radiation and androgen deprivation therapy (ADT), DeWeese says, and “one of the challenges is the lack of a reliable test allowing clinicians to monitor tumor response, both during and after radiation therapy.” The most commonly used marker, PSA, is not as useful in men receiving ADT, he adds, because “the PSA level is strongly suppressed by the ADT and is a less reliable surrogate for detecting active tumor.” Because these men receive ADT during the radiation and for up to three years afterward, “this limits the usefulness of PSA testing for an extended period of time, during which the window for curative therapies may close.” What’s needed, the scientists believe, is an “accurate, noninvasive monitoring test to guide early implementation of salvage strategies aimed at increasing the proportion of patients cured of their disease.”

Research done by their group and

others has shown that prostate cancers “nearly universally harbor stable, cancer-specific changes of the DNA. This modified DNA can be detected in urine and blood specimens,” says DeWeese. “We hypothesize that genome-wide assessment of these cancer-specific DNA changes in the blood and urine of prostate cancer patients, using technology developed by our group, called qMBD-seq, will allow for more helpful and accurate tracking of the cancer and the response to therapy in these high-risk men receiving radiation therapy and ADT.”

In an early-phase clinical study, DeWeese, Yegnasubramanian, and Mian are establishing the background levels of modified DNA in the urine and blood of men with no history of prostate cancer. “Then, we will quantify cancer-specific DNA abnormalities in the urine and blood of men known to have high-risk prostate cancer at multiple time points before, during, and after radiation treatment. These samples will be analyzed using our genome-wide qMBD-seq approach, allowing us to simultaneously characterize and quantify prostate cancer-specific DNA. This will allow us to predict which men have prostate cancer still present in their body after treatment, even if their PSA is very low or even undetectable.” ■

Telomeres and Prostate Cancer in African American Men

For years in *Discovery*, we’ve reported on the troubling facts — many of them determined from research done here at Johns Hopkins — that African American men are more likely to get prostate cancer, to have more or higher-grade cancer than was originally suspected, to have cancer recurrence after treatment, and more likely to die of their cancer compared to white men. (One of these stories features Ted Schaeffer’s latest findings on Page 9.) Even when

diagnosed with very low-risk prostate cancer, African American men are more likely to develop a tumor in a different location, often in the anterior of the prostate, and these tumors are often high-grade and large in volume.

But why? What makes African American men, out of all men in the world, the group hardest hit by prostate cancer? Christopher Heaphy, Ph.D., Assistant Professor of Pathology, the Dr. and Mrs. Peter S. Bing Scholar, offers new insight. “Our laboratory studies long stretches of specialized DNA located at the ends of every chromosome,” he says. “These protective caps of the chromosomes are called telomeres, and they stabilize the ends of the chromosomes.” Telomeres are a lot like aglets — the little bits of plastic at the tips of shoelaces — in that they protect chromosomes from getting frayed and tangled. “Unfortunately,” Heaphy says, “a portion of telomeric DNA gets lost from each chromosome end every time a cell divides. If too much of it is lost, then the telomere loses its protective function, and the cell’s chromosomes become unstable.”

Heaphy and colleagues, Elizabeth Platz, Angelo De Marzo, and Alan Meeker, recently conducted a large study of the removed prostate tissue in men who underwent radical prostatectomy. “Using a robust assay, we measured telomere lengths specifically in prostate cancer cells, and also in normal cancer-associated prostate stromal cells,” he explains. “Interestingly, we found that men with telomere abnormalities in both their prostate cancer cells and in the normal stromal cells nearby had a 14-fold higher risk of dying from their disease.” Heaphy notes that these findings were independent of the usual markers — Gleason score, stage of cancer, and PSA levels — that help determine prognosis. Now, in a follow-up collaboration with Ted Schaeffer, Heaphy and colleagues are proposing “that critical telomere shortening is an important causal factor

in prostate tumor formation.” They suspect that “African American men either inherit short telomeres, or they display an increased propensity for telomere shortening within the prostate.”

Heaphy believes these telomere abnormalities may be a “distinct underlying biological factor” that can help explain the racial differences, including where tumors are likely to develop, and the greater severity of prostate cancer in African American men. The next step is to study what he calls the “mechanistic underpinnings” of this link between telomere abnormalities and prostate cancer racial disparities, “with the goal of opening new avenues for the development of preventive and therapeutic interventions.” ■

Helping Men Navigate Treatment and Screening

“My PSA is a little high. Should I get a biopsy?”

“I have prostate cancer but the doctor says it’s slow-growing. Should I go ahead and get it treated?”

“I’m 79 years old. Should I still get screened for prostate cancer?”

“I’m 41 years old. I got my PSA tested last year. Should I get screened for prostate cancer this year?”

Although our ability to treat prostate cancer has never been better, making decisions about prostate cancer screening and treatment have never been more confusing — “for patients, their doctors, and even for population health managers, whose job is to design and monitor cancer screening and treatment programs,” says Scott Zeger, Ph.D., The Nancy and Jim O’Neal Scholar. The water is muddy, and Zeger, a professor of biostatistics, and urologist H. Ballentine Carter, M.D., are hoping to add a little clarity.

With support from the Patrick C. Walsh

Prostate Cancer Research fund, they are launching a pilot study, “a collaboration between prostate cancer medicine and statistical science to build a probability model,” says Carter. The model will take into account the screening and treatment decisions faced by Johns Hopkins patients, make estimates from published and patient data, and use these findings to “better understand where clinical interventions can maximize the chance of positive prostate health outcomes.”

Currently, “it is challenging at both the level of the individual patient and also of populations,” says Carter, “because men who do decide to be screened then face decisions about whether to have a biopsy if their PSA is a little high and, if cancer is found, which treatment option to pursue.” All of these decisions, Zeger adds, “entail weighing potential benefits against potential harms. “A clear understanding of the potential harms and benefits of the options at each decision point will be critical to help men decide what they should do.” ■

Developing a “Liquid Biopsy” of Metastatic Prostate Cancer

Although there have never been better therapies for metastatic prostate cancer, says Ben Ho Park, M.D., Ph.D., the Irene and Bernard L. Schwartz Scholar, eventually drug resistance still develops and the cancer continues to grow. Thus, scientists must find the genetic causes that drive these processes, says Park, an Oncologist with a joint appointment in the Department of Chemical and Biomedical Engineering. “Recently, there has been renewed interest in androgen receptor (AR) mutations that are found in metastatic sites after hormonal therapy,” he notes. “The problem with these studies is that often, just one biopsy at a single site has been used to document whether AR mutations are there or not. But

because there are many different types of cancer cells involved, a single-site biopsy is likely not enough to give us the correct picture.”

All cells, including cancer cells, shed DNA into the bloodstream. “Only recently has technology matured to the point where we can accurately identify these cancer DNA molecules in the blood,” Park says. He believes looking at this “circulating plasma tumor DNA,” called ptDNA, may give better insight into the true nature of the cancer cells that need to be treated. Using a technology called droplet digital polymerase chain reaction, or ddPCR, “we are able to detect cancer mutations in the blood with exquisite sensitivity and specificity — giving us a liquid biopsy, which promises to overcome the constraints of tissue biopsies.”

However, the technology for ptDNA analysis is not yet ready for routine clinical practice, Park says. “Most significantly, the variable and exhaustible amount of plasma DNA that can be obtained per patient sample can be a limiting factor.” In a study with scientist Paula Hurley, Ph.D., the Beth W. and A. Ross Myers Scholar, Park is hoping to find a way to “immortalize” plasma DNA by “merging existing technologies in a unique way, which will allow us to endlessly amplify plasma DNA with perfect fidelity.” If this proves successful, this plan will “significantly improve and impact the ability to move ptDNA forward as useful biomarkers” that will give scientists the specific rundown of the cells in a tumor — and suggest how best to kill them. ■

New Drug Selectively Kills Prostate Cancer Cells, and Works Even Better When Combined With Radiation

Venu Raman, Ph.D., and colleagues have identified a gene called DDX3. You probably haven't heard of it, but if it is as promising as Raman believes, you will be hearing more about it someday soon. Raman, who holds a joint appointment in the Department of Radiology and Radiological Science and in the Department of Oncology, is intrigued by DDX3 because "it is essential for the maintenance of many high-grade tumors, including those of prostate cancer," he says. When he and colleagues stained cancer tissue samples, they found that "35 percent of tumors with a Gleason score of more than 7 have an increased expression of DDX3." And this is important because "we have designed a drug, which we call RK-33, that neutralizes the function of DDX3." The result? Only the cancer cells die, and the normal cells are unharmed.

"We have designed a drug," called RK-33, that kills cancer cells, but leaves normal cells unharmed.

Even more exciting, says Raman, The Carolyn and Bill Stutt Scholar, is that when RK-33 is combined with radiation, "it produces a synergistic cell death effect on cancer cells. We are confident that the use of DDX3 as a biomarker, to determine which cancers should be treated with RK-33 and radiation, will not only significantly reduce the tumor burden, but also reduce many side effects of conventional treatment." When mice were treated with RK-33, they did not demonstrate any evidence of toxicity, which suggests that "we can expedite the use of RK-33 into the clinical setting." ■

What Allows Prostate Cancer to Invade Bone?

"While only a fraction of men diagnosed with prostate cancer die of the disease, prostate cancer remains the second leading cause of cancer death in American men," says Paula Hurley, Ph.D., the Beth W. and A. Ross Myers Scholar. This happens because some cancers leave the prostate and grow at distant sites — often, in bone. Why some cancers stay in the prostate and others are able to spread and establish themselves elsewhere is a question that scientists still haven't answered. But if they knew what the determining factors were, they would be better able to tell which men are at risk for developing aggressive, potentially lethal cancer.

Scientists know that certain non-cancerous cells that live inside prostate cancer play a role in whether the cancer stays or roams. Hurley, Assistant Professor of Urology and Oncology, and colleagues have recently shown that a protein called Asporin (ASPN) is highly expressed in normal cells that sit right beside prostate tumors. Further, "we have demonstrated that men who show ASPN expression in the prostate tumor at surgery are more likely to have recurrent prostate cancer." ASPN, it turns out, has also been shown to play a role in bone health. Hurley suspects that ASPN may help facilitate cancer growth in bone by inducing "osteomimicry" — allowing tumor cells to acquire traits of bone cells, which would let them survive and even thrive in bone.

In mouse studies, Hurley aims to learn more about how ASPN promotes the spread of prostate cancer to bone, and to find out whether ASPN induces prostate cancer cells to "express traits that are specific to bone cells." ■

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MORE BRADY UROLOGY CANCER NEWS



Bivalacqua: Test could be a much-needed alternative to invasive follow-up procedures.

Urine Test Can Detect Bladder Cancer Early

When bladder cancer reaches the muscles, it is often fatal. However, in its first stages, the cancer just perches on the lining of the bladder, and this is the time when it is most curable. But early detection is a problem, notes Trinity Bivalacqua, M.D., Ph.D., Director of Urologic Oncology. “Although we have a urine test that is able to detect high-grade, more advanced cancers of the bladder, its performance in detecting early precursor tumors that have the potential to become more aggressive is poor.” Several new urine tests have come on the market, but they haven’t proven reliably accurate or consistent, and so are not in widespread use.

“This test has great potential to save many lives.”

Unfortunately, the need for a better test has never been greater. Not only is more bladder cancer being diagnosed, but the vexing nature of this cancer is that it tends to come back after treatment. The best way now for urologists to detect and monitor bladder cancer is with

invasive procedures, including cystoscopy and transurethral bladder biopsy. “Because of the high rate of tumor recurrence, we have to perform frequent follow-up cystoscopy procedures,” says Bivalacqua, “but this results in an unacceptable rate of invasive procedures and ballooning costs. In the U.S., the management of bladder cancer has the highest cost burden per patient among all tumor types, with an estimated \$3 billion per year total cost to the health care system.”

Good news: Hopkins scientists have discovered a better test. It has to do with mutations in the promoter of the telomerase reverse transcriptase (TERT) gene. A multidisciplinary team of Hopkins scientists, led by George Netto M.D. a genitourinary pathologist and Professor of Pathology and Urology, along with Bert Vogelstein, Nickolas Papadopolous, Louis Diaz and Ken Kinzler, from the Ludwig Cancer Research Team, working closely with Brady urologists including Bivalacqua and Mark Schoenberg M.D., found a very high prevalence of TERT promoter mutations in a wide range of precursor bladder cancers. “These are the most common genetic alterations ever identified in early bladder cancer,” says Netto.

Could a test for TERT mutations also pick up the return of bladder cancer after treatment? The group looked for these mutations in a series of early tumors and also in follow-up urine samples from patients who developed recurrent bladder cancer and others who did not have recurrent cancer. Among patients whose tumors harbored TERT promoter mutations, the same mutations were present in follow-up urines in those who developed a recurrence but not in the urine of patients whose cancer did not recur.

“These exciting results strongly support the potential future analysis of TERT promoter mutations as a urine test that

can facilitate the early diagnosis of bladder cancer, before it spreads deep into the bladder wall, in patients at high risk for disease progression,” says Bivalacqua. “The test will also give us a noninvasive alternative to the many follow-up procedures we currently need to monitor our patients for recurrence of bladder cancer. This test has great potential to save many lives.” This work was published in *Cancer Research*. ■

For Complex Bladder Cancer Surgery, Brady Patients Do Better

There’s a lot to be said for a “high-volume” center — a hospital, usually a teaching institution, that treats many people who have the same condition every year. High-volume centers perform certain complex procedures so often that not only are the surgeons highly experienced at doing them, but the nurses and clinical staff who care for these patients are expert at attending to their specific needs.

Urologists at Johns Hopkins offer a number of treatment options for people with bladder cancer, including minimally invasive approaches such as robotic-assisted laparoscopic radical cystoprostatectomy, and open surgery. Trinity Bivalacqua, M.D., Ph.D., Director of Urologic Oncology, and urologists including Phil Pierorazio, M.D., and Christian Pavlovich, M.D., perform more than 100 radical cystectomy procedures a year. They also offer all types of incontinent and continent urinary diversions. “What they have found is that more experience is crucial for optimal and superior oncological and functional results,” says Bivalacqua.

Recently, a team of Hopkins scientists looked at the impact of hospital volume on the outcomes of patients who

underwent a partial or radical cystectomy as treatment for their advanced bladder cancer. “Historically, these procedures have been associated with a high rate of complications,” says Bivalacqua, who led the team.

Having surgery at Johns Hopkins, the highest-volume center in the state, was associated with decreased length of ICU stays, fewer in-hospital deaths and lower hospital fees.

Partial cystectomy: Urologist Max Kates, M.D., investigated complications associated with partial cystectomy using the Nationwide Inpatient Sample database. Most notably, he and colleagues found that for each additional partial cystectomy a hospital performed, the risk of in-hospital death decreased by 30 percent. They also showed that increased hospital volume was independently associated with decreased deaths in bladder cancer patients undergoing partial cystectomy. This work was published in *Urologic Oncology*.

Radical cystectomy: In a similar study, urologist Michael Gorin, M.D. investigated the outcomes of radical cystectomy in the state of Maryland. He and co-investigators found that having surgery at Johns Hopkins, the highest-volume center in the state, was associated with decreased length of ICU stays, fewer in-hospital deaths and lower hospital fees. “These data are in line with observations from other large studies,” says Bivalacqua. Unique to this report, after controlling for differences in the medical complexity of treated patients, the authors showed that having a radical cystectomy at Johns Hopkins resulted in improved outcomes and reduced costs. This study was published in the *Canadian Journal of Urology*.

“Combined, these two reports argue strongly in favor of performing complex bladder cancer surgery at high-volume centers of excellence such as Johns Hopkins.” ■



Allaf and Pierorazio: Many patients can be followed safely without the need for surgery.

Active Surveillance Proving Safe for Small Kidney Cancers

Although the incidence of kidney cancer has increased dramatically over the last few decades, research led by Brady physicians is showing that many patients can be followed safely without the need for surgery.

Five years ago, Brady urologists Phillip Pierorazio, M.D., and Mohamad Allaf, M.D., began the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) Registry, following patients with small, localized kidney tumors (4 centimeters or smaller, and confined to the kidney), who choose either active surveillance or immediate surgery. “The patients undergoing surveillance have done incredibly well,” Pierorazio says. “No one has died of kidney cancer.” More than 450 patients at Hopkins, Columbia University, and Beth Israel Deaconess Medical Center are in the Registry; of those, about 55 percent have chosen surgery, and 40 percent have chosen surveillance. About 5 percent of those in the surveillance group later opted for surgery. In the 1970s, about 30,000 Americans were diagnosed yearly with kidney cancer; that number has jumped to about 60,000 today, in large part because of increasing use of CT scans. But still, the number of annual deaths – between

10,000 and 13,000 – has remained unchanged, Pierorazio notes. “So we’re operating on all these people, but we have not significantly changed the mortality of this disease. Which begs the question, are all of these tumors of consequence?” Is there overtreatment of these cancers? Although several institutions have studied surveillance, the studies have been mainly retrospective. Hopkins is one of three institutions worldwide with this kind of prospective protocol.

“The patients undergoing active surveillance have done incredibly well.”

Once it escapes the kidney, cancer is fatal. Surgical cure rates for kidney-confined tumors are excellent – about 95 percent. And yet: “If you took everybody in this country with a small kidney tumor, anything 4 cm or less,” says Pierorazio, “upwards of 30 percent are benign lesions – not even cancer. Of the 70 percent left, half are low-grade, indolent tumors. They’re not ever going to cause a problem. That only leaves about a third that are potentially aggressive.”

Who can safely avoid surgery? Pierorazio and colleagues have come up with a score based on some key clinical factors. For example: Tumors that are close to the renal hilum tend to be more aggressive. Women are more likely to have benign tumors, and older people are more likely to have indolent tumors. The risk of metastasis is extremely low in tumors under 2 centimeters. Surveillance is better for people with heart problems, particularly congestive heart failure.

With urologist Mohamad Allaf, M.D., Pierorazio runs a clinic for people with small kidney tumors. All in one day, patients get an ultrasound and labwork, then meet with a physician. “For patients who decide they want surgery, it’s very easy. We offer basically every option there is,” including complex partial, open-incision and robotic procedures. Patients who choose surveillance receive ultrasound every six months for the first two years, then annually.

“The DISSRM Registry is just one of the programs that keep the Brady at the forefront of urologic oncology research,” says Trinity Bivalacqua, M.D., Ph.D., Director of Urologic Oncology. “These early results will undoubtedly define how small renal masses are managed in the future.” ■

Partial Nephrectomy Removes Cancer, Saves Kidney

“Diagnosis of kidney tumors is on the rise,” says Mohamad Allaf, M.D. Associate Professor of Urology, Oncology, and Biomedical Engineering, and Director of Minimally Invasive Surgery. “Most of these patients are being treated with complete kidney removal,” a procedure called nephrectomy. Although the procedure is common, the complications are nothing to take lightly: “In some instances this may result in kidney failure, cardiovascular side effects, and the need for dialysis,” Allaf explains.

But there’s another option, one that Allaf says is often overlooked: partial kidney removal, or partial nephrectomy. The operation offers the “best of both worlds,” in that it removes the cancer, but still saves the kidney. As surgical procedures go, it is technically complex, and an operation not very familiar to many surgeons. “Many surgeons who do offer it use open surgery, or only perform it on the smallest and least complex tumors.” This is why Allaf, who directs the Brady’s kidney cancer efforts, recommends that patients seek a second opinion. “There are about 60,000 new cases of kidney cancer per year in the U.S. and approximately 10,000 urologists. If averaged out, each urologist will see only six cases per year. Getting a second opinion at a busy center is critical,” he says. “Often, patients come to me after a surgeon has wanted to remove their entire kidney, or save the kidney but use a big flank incision, which is associated with hernia formation and other complications,”

Urologists at Johns Hopkins offer all treatment options to patients, including active surveillance for select tumors (see story on Page 22), minimally invasive approaches such as robotic-assisted laparoscopic partial nephrectomy, and open surgery when appropriate. Allaf and his team have one of the largest experiences in the world in robotic partial nephrectomy, performing more than 400 robotic kidney procedures a year. In two recent studies published in the *Journal of Endourology*, Allaf’s group studied the outcome of patients undergoing robotic partial nephrectomy at Johns Hopkins for complex tumors—those that are completely on the inside of the kidney, called intrarenal tumors, and those that are on the back of the kidney, called posterior tumors. The results indicated that in experienced hands, these patients did just as well as those with less complex tumors. In fact, important safety measures reported in those studies such as complication rates, ischemia times, and positive surgical margins were among the best in the published literature.

“We are very encouraged by our excellent results but still emphasize that we offer our patients all available options and reject a ‘one-size-fits-all’ approach. For patients needing surgery, we offer world-class care,” Allaf says. “In saving the kidney, we not only take care of the cancer, but we give the patients the maximal chance at not developing other complications including kidney failure, the need for dialysis, and other related problems. Some people come to us with one kidney, and in those patients, we’ve developed techniques that potentially can make it amenable to a minimally invasive robotic approach.”

Even difficult cases, such as multiple tumors, large tumors, cancer that invades deep into the kidney, unusual anatomy, or pre-existing kidney disease can be done with minimally invasive robotic techniques.

Even difficult cases, such as multiple tumors, large tumors, cancer that invades deep into the kidney, unusual anatomy, or pre-existing kidney disease — all of which previously were thought not ideally suited for a minimally invasive approach — can be done with minimally invasive robotic techniques. “It’s increasingly rare for us to have to remove the entire kidney for tumors less than 4 centimeters in size,” Allaf adds. For the team of urologists, anesthesiologists and nurses, “this is what we do, day in and day out, and to us, even very complicated cases are usually a straightforward robotic-assisted partial nephrectomy.” The average hospital stay is one to two nights. ■



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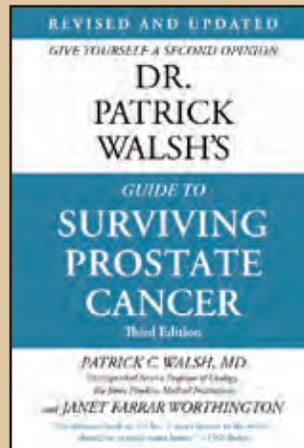
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Making a difference: Philanthropists Stephanie Cooper Greenberg and Erwin L. Greenberg.

Johns Hopkins Greenberg Bladder Cancer Institute Established

“Despite its prevalence and the number of lives lost every year, bladder cancer does not get the attention it deserves.” At Johns Hopkins, that’s changing in a big way.

\$45 million co-investment with the Johns Hopkins University, the Johns Hopkins Greenberg Bladder Cancer Institute has been created – the first bladder cancer institute in the history of the University.

The new Institute will bring together researchers from Hopkins and around the world who share a commitment to advancing the scientific understanding of bladder cancer and improving its treatment. “Our mission is to develop new clinical strategies for combating bladder cancer through intensive and innovative collaborative research,” says William Isaacs, Ph.D., the William Thomas Gerrard, Mario Anthony Duhon and Jennifer and John Chalsty Professor of Urology and Professor of Oncology, who is serving as the Institute’s Interim Director. “At Johns Hopkins, we are uniquely able to offer multidisciplinary expertise, with some of the world’s best scientists able to share ideas and tackle this disease from many different angles.”

The Institute will include faculty from the Brady Urologic Institute, the Sidney Kimmel Cancer Center, and the Departments of Radiation Oncology/Molecular Radiation Sciences and Pathology. The Hopkins members of the Institute will also collaborate with bladder cancer experts at other institutions, both national and international.

The Greenberg gift, which is the largest designated bladder cancer research gift ever given to Hopkins, was made through the Erwin and Stephanie Greenberg Foundation, whose philanthropy focuses on issues of poverty, education, and medical research. Erwin Greenberg, a Baltimore-area commercial real estate developer, serves on several nonprofit boards, including the Kimmel Cancer Center’s National Advisory Board, and Stephanie Cooper Greenberg serves on the advisory boards of the University’s Berman Institute of Bioethics, and of the Johns Hopkins Center for Innovative Medicine. ■

This year, more than 74,000 Americans will be diagnosed with bladder cancer and an estimated 15,000 will die of it. And yet, public awareness of bladder cancer is not nearly as great as it is for prostate cancer, breast cancer, or other higher-profile diseases. “Despite its prevalence, and the number of lives lost every year, bladder cancer does not get the attention it deserves,” says Trinity Bivalacqua, M.D., Ph.D., Director of Urologic Oncology.

At Johns Hopkins, that’s changing in a big way. Thanks to the generosity of Erwin L. Greenberg and his wife, Stephanie Cooper Greenberg and a