Active Surveillance: Good News for Men with Low-Risk Prostate Cancer

The Brady’s Active Surveillance program has reached a milestone: 20 years of carefully following men with low-risk prostate cancer. “What we have learned since 1995 can help many men with low-grade, low-risk prostate cancer, and their doctors, determine their best course of treatment,” says urologist H. Ballentine Carter, M.D., the Bernard L. Schwartz Distinguished Professor of Urologic Oncology, a pioneer in the active surveillance of prostate cancer. “There is increasing evidence that monitoring favorable-risk prostate cancer does not lead to worse outcomes when compared to immediate treatment,” says urologist H. Ballentine Carter, M.D., the Bernard L. Schwartz Distinguished Professor of Urologic Oncology, a pioneer in the active surveillance of prostate cancer. “There is increasing evidence that monitoring favorable-risk prostate cancer does not lead to worse outcomes when compared to immediate treatment.”

When the Active Surveillance program first started, “many urologists believed this approach was ill-advised for any man with a diagnosis of prostate cancer,” Carter notes, “for fear of losing the

Continued on page 4»

INSIDE THIS ISSUE:

From the Director
Changing Prostate Cancer ............... 2
Charred Food Bad, Veggies Good ... 6
Prostate Cancer in African American Men ............. 7
Immunotherapy for Prostate Cancer ..................... 8
Genetic Risk for Prostate Cancer ..................... 10
Attacking Early Metastatic Prostate Cancer .............. 18
Walsh Prostate Cancer Research Fund Awards
The Research You Have Helped Make Possible ............ 19
Bladder, Kidney, and Testicular Cancer News .......... 24

What Kind of Prostate Cancer Do I Have? Epstein Develops a Less-Confusing System

After all the worry — the elevated PSA, then the biopsy — the diagnosis is finally here. You just found out that you have prostate cancer and the Gleason score is a 3+3=6. What does that even mean? You look it up; the literature your doctor provided says that “the score is the sum of the most common and second-most common Gleason patterns.” Apparently, the lowest score is 2 (1+1) and the highest is 10 (5+5) — and you are a 6. That looks like you’re on the more significant end of the spectrum.

It’s not easy for most men to understand their prostate cancer stage right away, because the way Gleason scores are determined is just plain confusing. Epstein’s new system cuts through the numbers.

Wrong. Nobody gets a Gleason 2; they aren’t ever diagnosed on needle biopsies. “In fact, Gleason 6 is as good as it gets;” says urologist Patrick C. Walsh, M.D., University Distinguished Service Professor of Urology. It’s not easy for most men to figure this out right away, because the way Gleason scores are determined is just plain confusing — unless you’re a pathologist, seeing how a bunch of cells look under the microscope, and noticing which two combined patterns of cells are most prevalent.

Brady pathologist Jonathan Epstein, M.D., the Rose-Lee and Keith Reinhard Professor of Urologic Pathology, wants to make it easier for men to understand their prostate cancer

Continued on page 3»


CHANGING PROSTATE CANCER

“What does my diagnosis of prostate cancer mean?” For a century, our doctors and scientists here at the Brady have worked to answer that question on every level. Our discoveries have transformed the way organ-confined disease is treated and continue to bring new hope to men with metastatic disease. Our Active Surveillance program, pioneered by Bal Carter, has helped many men with slow-growing, small-volume disease avoid surgery safely; and now work by uropathologist Jonathan Epstein is actually changing the way the disease is diagnosed. For example, Gleason score 3+3 is its own category, Grade Group 1; Gleason 3+4 is Grade Group 2, and Gleason 4+3 is Grade group 3. There are only five groups, and Gleason score 8 is a distinct group, because those men have different disease than men with Gleason scores 9 and 10. The World Health Organization has accepted this system, and it will soon be used at hospitals everywhere.

In this exciting issue of Discovery, we’re proud to tell you about our latest work in immunotherapy, in dietary prevention, our work with robots, our advances in understanding genetic risk, our successes in molecular biology, and other breakthroughs including the successful imaging of individual cells of prostate cancer throughout the body—which opens up new targets for treating metastatic disease.

We also bring to you our continuing advances in diagnosis, treatment and active surveillance of kidney cancer, in refining treatment for bladder cancer, and a new advance in the laparoscopic treatment of testicular cancer.

Your generosity makes us able to do more, so that we can continue to improve the lives of people with urological diseases. Thank you for being our partners in discovery.

Best wishes,

Alan W. Partin, M.D., Ph.D.
Jakarshi Family Director and
Chairman of The Brady Urological Institute

Partin Honored

Alan W. Partin, M.D., Ph.D., the Jakarta Family Director and the Chairman of the Brady Urological Institute, received a Distinguished Contributions Award at the American Urological Association’s 2015 annual meeting. Presented by the AUA’s president, William W. Rohrer, M.D., the award cites Partin’s “contributions to science, most importantly, the creation of the ‘Partin Tables,’ which are used by urologists throughout the world.”

Continued from page 1 »

diagnosis. “Jonathan Epstein is unique in many ways, and one of them is that he does something that almost no other pathologist does—he actually talks to patients frequently,” says Walsh. “He understands how confusing this system is for most people to understand, and he wanted to fix this problem.”

Epstein’s new system, compared to the current Gleason system, is far simpler, with just five groups of cancer. One innovation is that it puts the confusing Gleason 7 score — which is very different, depending on whether it’s 3+4 or 4+3 — into two different groups. As Epstein explains: “The current prostate cancer grading system was developed between 1966 and 1974 by Donald Gleason. The system assigns histological patterns 1 through 5, adding the most and second-most common patterns with Gleason scores ranging from 2 to 10. There are more than 25 different possible combinations with this system.”

Doctors and scientists have tried to fix this; the Gleason system was revised in 2005 and again in 2014. “The current prostate cancer grading system is that the lowest score itself is still pretty confusing: a Gleason score 7 can represent mostly well-differentiated cancer, with a small component of poorly differentiated cancer — that would be Gleason 3+4–7. ‘It mostly poorly differentiated cancer with a small component of well-differentiated cancer,’ the score of Gleason 4+3–7. ‘Another weakness of the Gleason system is that the lowest score is now assigned a 6, although it is on a scale of 2–10.”

In a study of more than 25,000 men treated for prostate cancer at Hopkins and four other institutions, Epstein and colleagues verified a simplified system that cuts through the numbers. Epstein presented the new system at the 2015 meeting of the American Urological Association in New Orleans. “It’s more accurate than the current Gleason system, with only five grades,” Epstein says, “and the lowest grade is 1, as opposed to 6.” This also has the potential to reduce overtreatment of indolent prostate cancer, he notes. “We hope that this will permit more rational and less emotional decision-making; that men who are assigned a Grade Group 1 out of 5 will know that their cancer has an indolent nature. Tumors that are a pure Grade Group 1 at radical prostatectomy have no metastatic potential.”

This might also reassure men in this group who choose active surveillance. “Some men with Grade Group 2 tumors may also be candidates for active surveillance, or for radiation therapy instead of surgery depending on their age, extent of cancer, and general health.” In addition to making a clear distinction between the two Gleason 7 scores, the system separates Gleason 8 cancer from Gleason 9 and 10 tumors. “Gleason scores 8–10 are usually combined,” Epstein says. However, “although they are high-grade tumors, they still have significantly different prognoses.” Now, these are separated into Grade Groups 4 and 5.

Here is the breakdown for the new Grade Group system:

- **Grade Group 1** (Gleason score 2–3)
- **Grade Group 2** (Gleason score 3+4–7)
- **Grade Group 3** (Gleason score 4+3–7)
- **Grade Group 4** (Gleason score 8)
- **Grade Group 5** (Gleason scores 9–10)

Will this new system be coming soon to a hospital near you? Yes. It has been accepted by the World Health Organization, and will be used in conjunction with the current system “until it becomes widely accepted and practiced,” says Epstein.

Radical Prostatectomy with Two Robots

What could make robot-assisted laparoscopic radical prostatectomy even better? How about another robot? Dan Stanioveci, Ph.D., Director of the Urology Robotics Program, and his world-renowned Robotics Laboratory have designed, built and tested a robot that maneuvers an ultrasound probe. This novel robot, called the transrectal ultrasound probe manipulator (TRUS robot, for short), allows surgeons to do something very important: See — and preserve, if no cancer is there — the tiny neurovascular bundles, which contain the nerves that are needed for erection, and are critical for recovery of sexual potency.

In a recent study, working with surgeon Misop Han, M.D., the David Hall McConnell Professor in Urology, and other Brady colleagues, Stanioveci tested the TRUS robot in a brand-new procedure called tandem-robot assisted laparoscopic radical prostatectomy, or T-RALP, done in 49 men whose average age was 59. The TRUS robot was used together with the daVinci surgical robot, to take ultrasound images “at critical points of the operation,” says Stanioveci.

The results showed that the T-RALP is safe and feasible, and that it “can potentially improve the visualization of the neurovascular bundles, and subsequently improve postoperative recovery of potency in men.”
Active Surveillance: A Tailor-Made Approach?

“In our program, we have generally recom-
mended relatively intense monitoring, with prostate biopsies done annually for men
who had Gleason score 6 cancer in no
one-third of these men had “low-risk”
prostate cancer or developed advanced
disease. This is thought to be because the
first biopsy may have captured the
higher-grade cancer that was there all the
time. Grade reclassification also occurred,
outside those first two years, in men with “low-
risk” instead of a “very low-risk” disease.
Another striking finding: With each prostate
biopsy that showed the cancer was holding
steady, still indolent, and with no change
in grade, the risk of finding more aggressive
disease fell by 30 percent.

Carter and colleagues have used these
findings to construct a risk calculator for
men on active surveillance. It will be available
soon, and will be easy to use, Carter says.

“Our results show that men who are
diagnosed with very low-risk or low-risk
(prostate cancer and surgery. All this has changed,
men may be deferred for several years. “Today, about 30 to 40
treatment. “Today, about 30 to 40
men are monitored faithfully,
with regular follow-up visits
and biopsies. Our findings show that
men with both very low-risk and low-risk
cancer may be deferred for several years. “Today, about 30 to 40
women diagnosed with favorable-risk prostate cancer should
think carefully before pulling the trigger
to treat their cancer,” states Carter.

“They may well be a candidate for no
immediate treatment and just careful
monitoring.” Better understanding of
the kind of cancer a man has
whether his risk of having aggressive
disease is lower or higher — means
that more men are opting to wait on
treatment. “Today, about 30 to 40
percent of men diagnosed with favorable-
risk prostate cancer are being managed
with surveillance, compared to fewer
than 10 percent in 2010.”

Chan Receives Award

A big award for Daniel W. Chan, Ph.D.,
Director of the Chemical Chemistry
Division and Center for Biomarker
Discovery and Translation, and
Co-Director of the Pathology Core
Laboratories: Chan was selected to
receive the Human Proteome
Organization’s very first HUPO
Translational Proteomics Very Award.
This honor, presented at the 2015
HUPO Congress in Madrid, is “the most
important proteomics award
in my career,” says Chan.

“People with prostate cancer, sessions are
devoted to prostate cancer, managed in some patients. It, and others
like it being used in Europe, have caught
the prostate cancer cells specifically.”

Previously in
PET agent called DCFPyL. Pomper is
excited about the potential for DCFPyL
to help men throughout the prostate
cancer spectrum. “This agent has vastly
higher sensitivity and specificity, and
it provides sharper images,” he says.

“That will enable us to expand the use
of imaging, not only to primary disease,
but to see if the disease has returned
after initial treatment, to help make
treatment more accurate, and even as a
monitoring tool for men on active
surveillance. We believe that the images
we are getting are the clearest ever
obtained for prostate cancer in a human
being.” As a bonus, PSMA is also
expressed in the blood vessels
of other types of cancers, this technique
may also help spot other tumors,
including certain forms of kidney
cancer, he adds.

Pomper and colleagues recently
published their results in Molecular
Imaging and Biology.
Charred Food Bad, Veggies Good for the Prostate

Those of us who love steaks and hot dogs on the grill were chagrined a few years ago, when scientist Bill Nelson, M.D., Ph.D., the Marion I. Knott Professor and Professor of Oncology and Director of the Sidney Kimmel Comprehensive Cancer Center, began investigating something called “PhIP.” PhIP (a short name for a long chemical compound) is found in meats cooked at high temperatures — think of charred burgers, or fried chicken. It is a “pro-carcinogen,” a chemical that turns into something that can attack and mutate DNA, and is known to cause prostate, breast, and colorectal cancer in rats. But there’s good news: It pays to eat your veggies. “When we fed rats tomatoes and broccoli along with PhIP, the animals lived longer, and showed reduced incidence and severity of prostate neoplasms (new, abnormal cell growth, particularly of PIN, prostatic intraepithelial neoplasia — funny-looking cells that are linked to prostate cancer), intestinal cancers, and skin cancers as compared to rats fed PhIP alone,” says Nelson. “This provides even more evidence that eating vegetables may protect against cancer-causing agents like those in overcooked meats.”

There is also a twist to the story: Food safety pays off, as well. Nelson, along with pathologist Angelo De Maro, M.D., Ph.D., and scientist Karen Sfanos, Ph.D., has also explored the idea that prostate cancer may involve a combination of “environmental insults” — bad things in the diet, plus something else that weakens the body, like an infection. They wondered whether chronic inflammation — caused by bacterial infection — would make a difference in rats that had consumed PhIP. Using a specific strain of E.coli, isolated from a patient with chronic prostatitis/chronic pelvic pain syndrome by urologist Anthony Schaeffer, M.D., and further studied by urologist Edward Schaeffer, M.D. Ph.D., the R. Christian Evesen Professor, they found, to their surprise, that the charred food plus the nasty bug (many people have E.coli in their gut and it is harmless, but some strains can get into meat when it’s processed, and can survive if the meat is undercooked) seemed to have a systemic effect, causing an increase in the development and progression of cancer in the skin and digestive tract. The rats that received the double punch of E.coli plus PhIP fared worse than rats that ate the PhIP alone. In one study, the bacteria- and PhIP-consuming rats developed more precancerous lesions within the prostate and might have developed even more problems — except they also died sooner.

In further experiments, Nelson, De Maro and Sfanos found that “when we inoculated PhIP-fed rats with E.coli in the prostate, the animals developed acute and chronic prostate inflammation out of proportion to that seen with PhIP ingestion or E.coli inoculation alone, and had more prostate neoplasms, intestinal cancers, and skin cancers. “This hints that prostate infections and dietary carcinogens might interact to promote chronic prostate inflammation and prostate cancers, and that prostate infections might augment carcinogen effects on other tissues, as well,” says Nelson.

Nelson, De Maro, Sfanos, and colleagues recently published two papers on these striking new findings in the journals PLOS ONE and Cancer Prevention Research.

Shorter Telomeres in Normal Cells Can Point to Prostate Cancer

Every time a cell divides, we lose a minuscule portion of the telomere’s DNA, and become more vulnerable to illness.

Brady scientist Alan Meeker, Ph.D., is one of the foremost experts on a tiny but very complicated subject: telomeres. These are bits of specialized DNA found at the ends of every chromosome. They are like little shields, tips that protect the chromosome from wear and tear — think of an aglet on a shoelace, keeping the strings from fraying. Every time a cell divides, we lose a minuscule portion of the telomere’s DNA; as we age, our telomeres get progressively shorter. “They’re a buffer between our chromosomes and the outside world, and as they shrink, we become more vulnerable to illness,” says Meeker.

Back in 2006, Discovery reported on Meeker’s discovery with Brady scientist Donald Coffey, Ph.D., The Catherine and J. Smith Mclitchie Distinguished Professor of Urology, that the shortening of telomeres is an important contributing factor to the development of prostate cancer, and that men who inherit short telomeres have a higher risk of developing cancer.

Since then, Meeker has continued to work with Hopkins scientists to learn more about telomeres, and with Christopher Heapy, Ph.D., he found that, in men who underwent radical prostatectomy, those with telomere abnormalities in both their prostate cancers and in nearby cells, and in nearby cells that otherwise appeared normal “had a 14-fold increased risk of dying from their disease.”

Next, “given these interesting results, particularly the presence of short telomeres in the nearby normal-appearing cells, we hypothesized that the presence of shorter telomeres in diagnostic biopsies would also be associated with risk of prostate cancer,” says Meeker. In collaboration with colleagues at the Johns Hopkins Bloomberg School of Public Health, Meeker and Heapy studied telomeres in normal cells in biopsies from men who received a placebo in a national prostate cancer prevention study, the Prostate Cancer Prevention Trial. “We found that men with short telomere lengths in their biopsies had a higher likelihood of aggressive prostate cancer compared to men who had normal telomere lengths,” says Meeker. These findings suggest that telomere shortening in normal-appearing cells may help predict the presence of prostate cancer. “In order to test this idea, we are validating these findings, and also performing studies to better understand the biology of the subset of cells with short telomeres within the prostate tumor microenvironment.”

This work was recently published in the journal, The Prostate.

A “Double Whammy” for Detecting Prostate Cancer in African American Men

Because of the groundbreaking research of urologist Ted Schaeffer, M.D., Ph.D., scientists know that prostate cancer is more aggressive in men of African descent than it is in Caucasian men. They also know, thanks to Schaeffer, that not only is cancer more aggressive in these men; it’s harder to find. Schaeffer discovered that African American men are twice as likely as Caucasian men to have aggressive cancers develop in the anterior area of the prostate.

They discovered that not only are the cancers different, but the difference is potentially dangerous.

“If you think of the prostate as a house, and the rectum as the basement, we come up through the basement with the biopsy needle,” says Schaeffer. “In most Caucasian men, prostate cancer is located in the posterior part of the prostate, immediately adjacent to the rectum — so it’s basically on the first floor. But in African American (AA) men, aggressive cancers are hiding up in the attic, which is much more difficult to sample on an ordinary prostate biopsy. For this reason, many AA men are misclassified as having indolent disease — they are falsely reassured that their cancer is not the kind to worry about — and their diagnosis of aggressive cancer is delayed.”

Building on this work, Schaeffer has explored whether these cancers themselves are different — not just in location, but in their molecular makeup. In other words, “are the fundamental building blocks different in tumors that begin in the posterior location?” To find out, Schaeffer and colleagues examined the genetic codes of more than 100 prostate cancers from both anterior and posterior locations, in both AA and Caucasian men. “Caucasian men can develop anterior tumors that are aggressive, but they are more common in AA men.” They discovered that not only are the cancers different, but the difference is potentially dangerous.

“We found that these anterior cancers make less PSA than the posterior tumors do, and that anterior cancers are less dependent on male hormones for their growth than posterior tumors are. This was true in men of both races, but had the strongest association in AA men.”

The problem, Schaeffer says, is that “we use PSA levels as a screening tool to look for cancers. So that this may be a ‘double whammy’ for men with anterior cancers: First, anterior cancers are already harder to detect with traditional prostate biopsies. Second, if they make less PSA, men with these tumors may not be offered a biopsy at the earliest possible stage,” because a doctor might look at the PSA number and think all is well.

“We don’t yet have a biomarker that is capable of specifically picking up an anterior tumor, but this is certainly a dream of mine,” Schaeffer adds. “However, the advent of MRI-ultrasound fusion biopsies shows significant promise in picking up these hard-to-finders.”

Schaeffer believes that all men who have had a negative prostate biopsy should undergo an MRI scan, to make sure there isn’t an anterior tumor lurking in the prostate’s forbidden attic. “For men of African descent with an elevated PSA may want to consider getting an MRI as a first step.”

Congratulations to Schaeffer

One of the things the Brady is most proud for is training the next generation of leaders in Urology. In exciting news, urologist Edward Schaeffer, M.D., Ph.D., has been appointed the new Chair of Urology at the Northwestern Feinberg School of Medicine in Chicago. He will be the Edmund Andrews Professor of Urology. “This is a great and well-deserved opportunity for Ted,” says Alan W. Partin, M.D., Ph.D., Jakarsi Family Director of the Brady Urological Institute. “His leadership, scholarship, mentorship and fellowship will be greatly missed. We congratulate him on his contributions to the Brady and on this outstanding recognition of his achievements.”

Schaeffer, Schaeffer, left, is the Edmund Andrews Professor, chair of urology, one of the charter founders of the Patrick C. Walsh Prostate Cancer Research Fund. In his years at the Brady, Schaeffer has “commandingly combined surgical acumen and scientific discovery,” says urologist Patrick Walsh, M.D.
**Immunotherapy Plus Short-Term Hormonal Therapy: Promising Results**

**But when we gave immunotherapy just before hormonal therapy, the results were striking. A significant proportion of animals never developed castration-resistant disease.**

The body’s own immune system can pose some stunning successes. When the body decides to recognize something as an enemy and the full power of its militia kicks in, the effect can be powerful — too powerful in the case of an autoimmune disease, and not powerful enough in cancer. Although the idea of cancer-targeted immunotherapy has been around for decades, only recently has it begun to show some stunning successes in melanoma, lung cancer, kidney cancer, and bladder cancer. In prostate cancer, however, success has come more slowly. Brady scientist Charles Drake, M.D., Ph.D., an immunologist and one of the thought leaders in the field, is taking a new tack.

“Results of immunotherapy in prostate cancer have been less impressive than in other diseases, with immune checkpoint (see side story) blockade showing little evidence of response in several clinical trials,” Drake says. “But based on our published data, we hypothesized that combining immunotherapy with hormonal therapy — earlier in the course of disease — before the cancer stops responding to hormonal therapy — could lead to better outcomes.”

Using an animal model that “reliably responds to castration,” or androgen ablation, the medical shutoff of testosterone, “but later develops castration-resistant disease, we tested the relative timing of hormonal therapy and immunotherapy,” Drake explains. “Immunotherapy alone, either early or late in the disease’s course, was ineffective. But when we gave immunotherapy just before hormonal therapy, the results were striking. A significant proportion of animals never developed castration-resistant disease.”

There are different types of immune checkpoint inhibitors. Drake and colleagues tried PD-1 blockade, and found that it was “unimpressive.” Then they tried CTLA-4 blockade, which was more promising, and a new compound was better still. A CTLA-4 antibody that targets and depletes regulatory T cells (which suppress the immune system) “was the most efficacious immunotherapy we found,” says Drake. “Taken together, we hope that these promising results will drive a translational clinical trial, in which anti-CTLA-4 is administered in combination with a short course of hormonal therapy in men with high-risk disease progression. It’s worth noting that the PSA has returned and is on the rise!”

Drake and colleagues presented these results at the American Society for Cancer Research’s annual meeting in 2015.

Cryotherapy Plus Immunotherapy May Equal New Hope for Men with Metastatic Prostate Cancer

**Think about aggressive treatment for metastatic prostate cancer, and what comes to mind? Most likely, it’s not cryotherapy or immunotherapy — or putting these two therapies together. But that may soon change, if a small trial at Johns Hopkins is as promising as Brady scientists think it may be.**

“CTLA-4 and PD-1 are an immune checkpoint pair that targets the molecule CTLA-4. Remember, the immune system has several checkpoints to protect itself against cancer cells. However, those tumor-dismantling immune cells are often held back by a series of molecules known as immune checkpoints,” Drake says. “In order to break these checkpoints, Drake and colleagues tried PD-1 blockade, and found that it was more promising, and a new compound was better still. A CTLA-4 antibody that targets and depletes regulatory T cells (which suppress the immune system) “was the most efficacious immunotherapy we found,” says Drake. “Taken together, we hope that these promising results will drive a translational clinical trial, in which anti-CTLA-4 is administered in combination with a short course of hormonal therapy in men with high-risk disease progression. It’s worth noting that the PSA has returned and is on the rise!”

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**Will I Get Prostate Cancer? New Study Calculates Genetic Risk**

For more than a decade, investigators led by William Isaacs, Ph.D., the William Thomas Garrard, Maria Anthony Dalton and Jennifer and John Chalsty Professor of Urology, have made tremendous progress in discovering major genetic factors linked to an inherited risk of prostate cancer. In fact, a decade before that, Brady investigators led by Isaacs and urologist Patrick C. Walsh, M.D., the William and Jennifer and John Chalsty Professor of Urology and urologist Patrick C. Walsh, M.D., have discovered include common and rare altered stretches of DNA — these men who had father had prostate cancer would be at an elevated risk of developing prostate cancer, but a man whose father, brother, and grandfather had prostate cancer would be at an even higher risk.

In the study, Isaacs, Xu and Helfand examined DNA samples from men with a family history of prostate cancer to determine the number of risky SNPs — altered stretches of DNA — these men inherited. “Interestingly, although most of these men carried more genetic risk factors than men without a family history, some men carried less,” says Isaacs. “These men were more likely not to develop prostate cancer than men without a positive family history. Indeed, the results of this study indicate that not all men with a family history of prostate cancer have equivalent risk.”

In fact, Isaacs continues, there is a wide range of risk, “and this can be estimated through measuring prostate cancer risk SNPs to calculate a genetic risk score.” This study has been submitted for publication.

Additional studies are needed to validate these findings, he adds, but this study provides a strong basis for developing a simple and inexpensive test to assess differences in prostate cancer risk among sons and brothers of men with prostate cancer. “Such an assessment could be useful in identifying men who would most likely benefit from earlier and more frequent disease screening.”

The results of this study indicate that not all men with a family history of prostate cancer have equivalent risk.

**Surviving Prostate Cancer: Good News for Radical Prostatectomy Patients**

So you had radical prostatectomy and things have been going pretty well. You feel good, and your PSA remains undetectable. It’s been several years now, are you out of the woods?

“Overall, men are highly unlikely to die from prostate cancer after surgery — even men with high-risk prostate cancer. If you do not experience recurrence for several years, your likelihood of survival for 10 more years is outstanding.”

**MicroRNAs: Genes that May Make Radiation and Chemotherapy More Effective**

Your dishwasher is broken again. You’ve kept it going, but maybe you’ve fixed it too often, maybe it needs to go. On the molecular level, your body faces similar dilemmas all the time when it comes to fixing damaged DNA. DNA is a precious thing, and the body works hard to keep it in good shape, but there’s a delicate balance, explains Brady scientist Shawn Lupold, Ph.D., the Frank Hinman Scholar: “Too little DNA repair can lead to an accumulation of changes — to uncontrolled cell growth, cancer development, or even cancer progression. On the other hand, too much DNA repair can be detrimental, too, if it helps cancer cells resist treatment like chemotherapy or radiation.”

Although cancer biologists know a lot about how to work with and around some of the body’s DNA-fixing mechanisms, there’s a new repairman in town, genetically speaking: A newly discovered class of genes called microRNAs. Lupold has been studying these genes and their role in the development and progression of prostate cancer with other Brady scientists, including Theodore L. DeWeese, M.D., Ph.D., the Sidney Kimmel Professor and Director of Radiation Oncology and Molecular Radiation Sciences. Although what microRNAs do is very complicated, and is still not fully understood, basically they send messages that produce action. “Each microRNA gene encodes a short RNA transcript that can act by actively turning off the synthesis of specific proteins and enzymes,” says Lupold. This led to an over 50-percent increase in prostate cancer cell sensitivity to ionizing radiation. Most importantly, we demonstrated that miR-890 specifically targets and inhibits an expression of multiple DNA repair genes and pathways.

They were looking for a new weapon that would not only make radiation therapy more powerful against prostate cancer, but would also hinder the cancer cells’ ability to recover from the attack.

In laboratory studies, the team injected the microRNA into established prostate tumors in mice, and two days later treated the animals with radiation therapy. “The tumors treated with miR-890 were significantly reduced in size and growth when compared to controls,” says Lupold. The next step, currently being worked on by Lupold and DeWeese, is to find the best way to deliver these microRNAs to prostate cancers, “with the ultimate goal of selectively sensitizing prostate cancer tumors to radiation and chemotherapy, while sparing the healthy tissues right next to the cancer.” In other studies of microRNAs, Lupold’s lab is exploring the role of these genes in other aspects of prostate cancer, such as androgen signaling.
Although PIN shares many hallmarks of tissue with this finding to make sure cancer cells were not missed the cancer cells were once again susceptible to hormonal therapy. The treatment had a double impact: After being bombarded with testosterone, prostate cancer cells were once again susceptible to hormonal therapy. These results were promising enough for Denmeade to received funding from both the National Institutes of Health and the Department of Defense’s Prostate Cancer Research Program to perform more clinical studies at Johns Hopkins. He and colleagues are testing this tumor in larger groups of men with prostate cancer that become resistant to standard hormone deprivation treatments. “Our goal with these clinical studies is to establish a role for high-dose testosterone as an inexpensive treatment that could improve quality of life, reduce disease burden and potentially reverse therapeutic resistance in men with advanced prostate cancer,” he says. “We hope to establish this as an effective therapy that can improve survival, overcome resistance to hormonal therapy, and meaningfully improve quality of life, functional activity, and sexual function in men with castrate-resistant prostate cancer!”

Denmeade was the principal investigator on the pilot study. Co-authors on the paper include Michael Schweizer, Emmanuel Antonarakis, Hao Wang, Seun Ajiboye, Avery Spitz, Haiyu Cao, Jun Luo, Michael Hafrner, Sripratima Vegnasubramanian, Michael Carducci, Marin Eisenberger, and John Isaacs.

Based on this observation, Denmeade and colleagues recently carried out a pilot clinical trial that showed that a monthly injection of high-dose testosterone could be safely given to men with castrate-resistant prostate cancer, and that it produced a therapeutic benefit in some men. These exciting findings were published in the journal, Science Translational Medicine. In addition, Denmeade says, “we observed that after treatment with high-dose testosterone, in most cases the prostate cancer cells became re-sensitized and were no longer resistant to treatments that Level out block testosterone.” In other words, the treatment had a double impact: After being bombarded with testosterone, prostate cancer cells were once again susceptible to hormonal therapy.

Boosting Testosterone NotShown to Raise Prostate Cancer Risk

Testosterone therapy was not found to increase PSA levels, or to promote the occurrence of prostate cancer.

For Men with Advanced Prostate Cancer: New Hopkins Test Can Tell If Some Drugs Won’t Work

For the first time, a blood test is available to help men with advanced prostate cancer determine if certain medications will work — or if they can avoid the trouble and cost of taking expensive drugs that won’t help their cancer.

This test, developed and tested at Johns Hopkins, promises to predict treatment response and resistance in men with prostate cancer that no longer responds to standard hormonal therapy.

“This is a major milestone.”

The test targets a faulty androgen receptor (AR) molecule called AR-V7, discovered in 2008 by Brady scientist Jun Luo, Ph.D. "This is a major milestone,” says Luo, who also pioneered the first AR-V7 blood test in his research laboratory. “Transforming a discovery and moving a test from bench to bedside has been a major challenge historically.”

That the test is available now to patients at the Brady represents several victories — of collaboration among scientists and physicians in several disciplines, and of Brady philanthropists who saw a need and responded with what urologist Patrick Walsh, M.D., calls “an emergency influx of generosity.” Walsh, University Distinguished Professor of Urology, notes that “the Brady Institute itself wouldn’t have been possible without private philanthropy — starting with a large endorsement from James ‘Diamond Jim’ Brady a century ago. Time after time, friends of the Brady have stepped up in support and_GATE". This concept in larger groups of men with prostate cancer that become resistant to standard hormone deprivation treatments is to establish a role for high-dose testosterone as an inexpensive treatment that could improve quality of life, reduce disease burden and potentially reverse therapeutic resistance in men with advanced prostate cancer.”

For Castrate-Resistant Prostate Cancer: High-Dose Testosterone

Hormonal therapy takes away a driving force of prostate cancer — testosterone. It can work well for many years, but eventually the prostate cancer cells figure out how to adapt to the low-testosterone environment, and they begin to grow. But studies in the lab of Brady scientists John Isaacs, Ph.D., and Samuel Denmeade, M.D., have shown that these ‘testosterone-deprived prostate cancer cells can be paradoxically killed’ by treatment with something they didn’t expect — high amounts of testosterone, says Denmeade.

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The study that led to this new AR-V7 test began with a pilot clinical trial that was conducted in the Molecular Diagnostic Laboratory, led by James Eshleman, M.D., Ph.D., Professor of Pathology, in conjunction with Luo’s laboratory. “We walked through every bit of detail of this test,” Eshleman says, a complex process, “and carried out a complete analysis to justify using the test on men with advanced prostate cancer.” The Molecular Diagnostic Laboratory at Hopkins is a CLIA-certified lab. (Any facility that performs laboratory tests on human specimens for the purpose of diagnosis or treatment is required by Federal law to have a CLIA certificate, and Medicare requires the CLIA certificate number before any claims can be processed.)

For men with advanced cancer that has become resistant to hormonal therapy, there are now six FDA-approved drugs that have been shown to improve survival.

“We ultimately hope that biomarker tests such as AR-V7 will help clinicians decide which among these drugs in a more rational manner,” says Emmanuel Antonarakis, M.D., Ph.D., Associate Professor of Oncology, who was the clinical lead investigator on this project. “Having a robust clinical test for measuring AR-V7 in blood is only the first step, however.” Antonarakis cautions that further prospective clinical trials will be required before the AR-V7 test is clinically validated and before information from the test can be used to guide treatment in men with advanced prostate cancer.

The AR-V7 blood test offered by the Molecular Diagnostic Laboratory has not yet been approved by the FDA and is available only at Johns Hopkins. For more information on how to request this test, please contact: Katie Beierl, molecu- larpathressults@jhmi.edu.
Don Coffey: the Man, the Movie

You’ve seen him many times on the pages of Discovery. He’s a scientific legend, here at the Brady, throughout the world of urology, and beyond, as the scientists he has trained and inspired began mentoring their own postdoctoral fellows and students. Now you can see him on the big screen — or someday soon on the small screen — in the role of Don Coffey, a remarkable man who first had a dream — and he was invited to provide the very first paper to launch the Asian Journal of Urology. **Potential New Pathway to Kill Prostate Cancer**

“This pathway has been considered untouchable, and efforts have not been invested to exploit it as an avenue to deactivate cancer cells. But our research has proven otherwise.”

There is a brand new way to target cancers, and cancer biologist Mariikki Laiho, M.D., Ph.D., the Willard and Lillian Hackerman Professor in Radiation Oncology, is one of only two scientists in the country funded by the National Institutes of Health to work on it. It’s called RNA polymerase I transcription.

This adventure in new science began when Laiho’s group discovered a small synthetic chemical molecule, called BMH-21, and showed that it has a unique way of killing cancer cells. “We learned that the molecule is a novel inhibitor of RNA polymerase I,” she says. “RNA polymerase I transcription is an intricately coordinated transcriptional program. It is highly activated and insufficiently controlled in cancers, but despite its ability to support cancer growth, it has received little attention as a possible new target for therapy.”

Transcription in this case means “reading the DNA into RNA, that is, converting the universal genetic code into a new biomolecule, RNA,” says Laiho. “RNA polymerase I drives a fundamental process that synthesizes the RNA component for the ribosomes (tiny factories inside cells where proteins are made, and here, essential for making cellular proteins). These building blocks are necessary for the life and health of cells. For this reason, this pathway has been considered untouchable, and efforts have not been invested to exploit it as an avenue to deactivate cancer cells. But our research has proven otherwise.”

Laiho’s findings suggest the promise of inhibiting RNA polymerase I transcription in a potential new class of cancer-fighting drugs. “We have shown that it has therapeutic benefit, and it is well-tolerated in preclinical models. We hope that our findings will invigorate basic science efforts on RNA polymerase I transcription. We still lack basic knowledge of the factors associated with this fundamental process and their regulation.”

Laiho believes BMH-21 has “particular relevance for the treatment of prostate cancers,” and it is turning her work toward developing a first-in-class nucleolar drug. Her team has received the Harrington Discovery Institute’s Harrington-Scholar Innovator Award and the Prostate Cancer Foundation Global Challenge Award for this work. Laiho and colleagues are now exploring the role of BMH-21 in advanced prostate cancer.

**Two Non-Cancerous Causes for Higher PSA**

“How can prostate cancer screening be improved? Brady epidemiologist Elizabeth Platz, Ph.D., M.P.H., the Martin D. Abeloff, M.D., Scholar in Cancer Prevention and Prostatic Diseases, and colleagues hope that information from this study will one day help reduce unnecessary biopsies, ‘both for men who have never been screened, and men who have been screened and biopsied, but cancer was not found.’”

In another study, led by biostatistician Sarah Peekoe, Platz and colleagues looked to see whether testosterone affects PSA levels in the blood. “While we know that testosterone helps signal prostate cells to make PSA, no one has quantified the association between testosterone and PSA in the blood in a general population of men who haven’t been diagnosed with prostate cancer,” says Platz. In this study, the investigators looked at data from 378 men, between the ages of 40 and 85, who participated in the National Health and Nutrition Examination Survey, which ran from 2001 to 2004. “We only included men who did not have a prostate cancer diagnosis and had not had a recent prostate, rectal examination, cystoscopy, or known prostate infection or inflammation,” says Platz. The scientists found that men who had higher testosterone levels also had higher PSA levels. “We also found that the odds of having a clinically elevated PSA were greater among men with higher testosterone levels. Our findings may indicate that in prostate cancer screening, American men who have higher testosterone levels may be more likely to undergo unnecessary prostate biopsy,” flagged by their higher PSA.

“We are not advocating that men should have their testosterone measured at this time, we expect that knowledge of the testosterone-PSA association may help refine tools for clinical decision-making in men who have an elevated PSA.”

Platz and colleagues published the results of these two studies in *Prostate Cancer and Prostatic Diseases, and Prostate*, respectively.

Don Coffey: Awarded the American Association for Cancer Research’s highest honor.
New Tests Show Genetic Changes Linked to Aggressive Prostate Cancer

ERG is a troublemaker, a gene that may promote the growth of cancer. With PTEN out of the picture, it stars in its own episode of “genes gone wild.” Lotan’s team has worked with De Marzo and other Johns Hopkins investigators to develop test simple, inexpensive assays that show the status of PTEN and ERG in prostate tumors. In work recently published in Modern Pathology, Lotan and colleagues showed that men who have Gleason 6 tumors with PTEN loss are about three times more likely to be upgraded to Gleason 7 or higher at radical prostatectomy. Further, Lotan’s team showed that prostate tumors with PTEN loss are two to three times more likely to be lethal compared to tumors without PTEN loss, “even after adjusting for the usual clinical and pathologic signs we currently use to predict prognosis,” Lotan says. “Interestingly, PTEN loss is more tightly associated with lethal disease when the tumor does not have ERG gene rearrangement — suggesting a significant interaction between these important genes in the progression of prostate cancer.” Lotan recently presented these findings at meetings of the United States and Canadian Academy of Pathology, and of the American Association for Cancer Research. Validated tests developed by Lotan, De Marzo and colleagues are now being offered in the clinical lab at Johns Hopkins, and Lotan’s team is working with investigators from several other academic centers to develop these tests into FDA-cleared prognostic and predictive biomarkers.

Could “Nerve-Sparing Brachytherapy” Help Preserve Sexual Function?

The “neurovascular bundles of Walsh,” discovered by Patrick C. Walsh, M.D., are tiny, delicate, and important: they contain the nerves that control erection. “An unfortunate risk of any treatment for prostate cancer is that many men who undergo curative surgery or radiation will subsequently develop erectile problems,” explains radiation oncologist Danny Song, M.D. For men who undergo surgery, the nerve-sparing techniques discovered by Walsh have been shown to help preserve sexual function. But until now, “there has been no clear understanding of what exactly leads to this side effect in patients undergoing radiation,” says Song, who recently set out to change this. “Prior studies have attempted to answer this question by evaluating the dose of radiation delivered by the neurovascular bundles, which are tiny cables of blood vessels and nerves that run along the sides of the prostate. However, these studies have not shown a difference in erectile function when comparing patients who received high vs. low doses to these structures.” So Song took a different approach. In a recent study of 366 men who underwent brachytherapy (the implantation of radioactive seeds at precise points to kill prostate cancer), Song and colleagues measured radiation doses to various anatomic structures around the prostate.

“Patients who received lower doses to the cavernosal nerves had less risk of erectile problems.”

“At Last, a Desperately Needed Mouse Model of Aggressive Prostate Cancer

How do scientists develop a new treatment for prostate cancer? First, they need a safe way to test it before they even think about trying it in humans. Unfortunately, the tests available to researchers make it difficult to develop and test targeted immunotherapy and treatments for bone metastases, two areas of great need in prostate cancer therapies,” explains Brian Simons, D.V.M., Ph.D. “New drugs are currently tested primarily on xenografts — human cells grown in mice, without a functioning immune system. But if mice don’t have an immune system, they can’t very well serve as models for any treatment that requires the body’s own ability to fight disease. Another problem: “Very few of these models develop metastatic tumors,” which limits the development of treatments for bone metastases. If mice don’t have an immune system, they can’t very well serve as models for any treatment that requires the body’s own ability to fight disease.

Simons has developed a new laboratory model that has the potential to do a lot of good for men desperately in need of treatment for advanced prostate cancer. Working with Edward M. Schaeffer, M.D., Ph.D., the R. Christian B. Evensen Professor of Urology, and a team of investigators, he has come up with a mouse model of bone metastatic prostate cancer that has many features of very aggressive human prostate cancer. “When injected into mice, these cells frequently form bone metastases that initially respond to anti-androgen therapy, but then become castration-resistant tumors,” he says. Already, this model is being used to test new immunotherapy treatment strategies and imaging systems to detect bone metastases.
A New Way to Attack Early Metastatic Disease

There are bits of cancer that have spread, or metastasized, beyond the prostate, but not that many, and not at very many locations in the body. Cancer in this state is still vulnerable, and still responds to treatment. For example, “in patients with oligometastatic sarcomas or colorectal cancer, local radiation to the primary tumor combined with chemotherapy, can result in long term disease-free survival in between 25 and 40 percent of patients,” says Tran. “Our own clinical experience suggests an oligometastatic state exists in a subset of prostate cancer patients who may benefit from local radiation treatment to all sites of macroscopic metastatic disease.”

Picture, if you will, the bloodstream. It goes throughout the body, flowing in one direction. Cancer cells that make their way into the blood, like seeds floating on a river, leave the original tumor — the mother ship — and drift for a while, eventually coming to rest at a distant site, where they may start to grow. This is the generally accepted model of how cancer spreads. But Tran suspects that these circulating tumor cells (CTCs) get home-sick — that they pay an occasional visit back to the original tumor, or maybe visit one of their siblings that has struck out on its own and built a home. These visits are invigorating: “The CTCs become more robust,” he says, “and this cyclical process of CTCs interacting with more established cancer results in the release of signals that foster tumor growth.”

Like a domino effect, then, tumor growth leads to angiogenesis — the paving of new roads, made of blood vessels, to supply the tumor; angiogenesis is followed by immune evasion — the cancer mutates to dodge the body’s militia of immune cells — and ultimately, “the formation of new, microscopic metastases.” This theory of macroscopic metastases being self-seeding communal sanctuaries is supported by recent genomic data from studies of human prostate cancer cells, Tran says.

What’s the best way to target these little blobs of cancer? Tran believes the key is stereotactic ablative radiation (SBRT), “a highly focused, localized, high-dose radiation delivered in a hypofractionated course,” meaning in several large doses, spread out over several days. “It’s ideally suited for treatment of oligometastatic patients, and has shown high local control rates with minimal toxicity,” he says. “SABR effectively targets the microenvironment of tumors, and in melanoma patients, has been shown to have antimutator effects on the irradiated tumor and an abscopal effect — death of a shock wave, affecting areas not part of the original blast — on distant metastases when combined with other immune-system-stimulating agents.”

Tran is starting a multi-institutional study aimed at killing oligometastatic cancer through SABR and immune system-targeting agents. This program is partly funded by an award from the National Cancer Institute to radiation oncologist Ted DeWeese and Director of Nuclear Medicine Martin Pomper, and by a November-Prostate Cancer Foundation Challenge award to Tran, who is the principal investigator, and to urologist Ashley Ross, DeWeese, Pomper, Adam Dicker (from Thomas Jefferson University), Max Diehn (from Stanford University), Charles Drake, Hao Wang, Kenneth Pienta and Marius Eisenberg.

In 2015, among other honors and awards, Tran was appointed Clinical Director of Radiation Oncology and was named Associate Editor for the journal, Cancer Research.

Capturing Cancer Cells in the Bone, Years Before They Cause Trouble

Brady surgeons and scientists are working together, using a surgical technique pioneered by three of our urologists, to target potentially lethal prostate cancer before it has a chance to spread. “The key here involves what we call disseminated tumor cells, or DTCs,” explains Ken Pienta, M.D., the Don Coffey Professor of Urology and Director of Research. The 10-week program offers a stipend of $3,000. Housing is provided near the Johns Hopkins University, and shuttle transportation to the medical campus is free.

“This summer internship requires a full-time commitment,” says Pienta. “Interns should be prepared for long days and short weekends. But the experience is unparalleled.”

If you would like to support this wonderful program or even sponsor a student, please see the envelope in this issue of Discovery.
Read About the Research You have Helped Make Possible.

THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND

It’s been going strong for a decade now. 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 help us save lives with better ways to treat and prevent it. Applications are reviewed by a Scientific Advisory Board composed of noted Hopkins scientists and lay members. These awards wouldn’t have been possible without your help.

2015 Awardees

H. Ballentine Carter, M.D., The Carolyn and Bill Statt Scholar, Departments of Urology and Oncology
Misop Han, M.D., Ph.D., The Nancy and Jim O’Neal Scholar, Departments of Urology and Oncology
Sushant Kachhap, Ph.D., Department of Oncology
Anthony K.L. Leung, Ph.D., The Irene and Bernard L. Schwartz Scholar, Departments of Biochemistry & Molecular Biology and Oncology
Sangeeta Ray, Ph.D., The Dr. and Mrs. Peter S. Bing Scholar, Department of Radiology and Radiological Science
Linda Ross, M.D., The Peter Jay Sharp Foundation Scholar, Departments of Medicine, Oncology, and Institute for Cellular Engineering
Ashley Ross, M.D., Ph.D., The R. Christian B. Evensen Scholar, Departments of Urology, Oncology, and Pathology
Daniel Thorek, Ph.D., Department of Radiology
Raphael Viscidi, M.D., The Beth W. and A. Ross Myers Scholar, Departments of Pediatrics and Oncology
Hui Zhang, Ph.D., The Virginia and Warren Snowerin Scholar, Department of Pathology

Understanding Prostate Cancer Progression During Active Surveillance

Did the low-grade cancer somehow morph into high-grade disease, or did both low- and high-grade disease just happen to spring up together?

Urologist H. Ballentine Carter has done pioneering research in prostate cancer for decades, but he’s never talked about it like this. Think of low-risk prostate cancer as a turtle, intermediate-risk cancer as a rabbit, and high-risk cancer as a bird. “The classification depends in large part on the cancer grade,” he says. “If turtles, rabbits, and birds were put into a fenced area (the prostate), the turtles would never leave, or spread to other parts of the body. The rabbits would sometimes leave, and the birds would often leave.”

Carter has been thinking about the different risk levels of prostate cancer particularly as it has to do with low-risk cancer — the men who qualify for the Active Surveillance program, which he began 15 years ago and continues to lead. With funding from the Patrick C. Walsh Prostate Cancer Research Fund, Carter has teamed up with some impressive Hopkins co-investigators — geneticist William Isaacs, pathologists Angelo De Marzo, Srinivasan Vigneswaran, Jonathan Epstein and Michael Haffner, and mathematical analyst and scientist Sarah Wheelan. “The purpose of this project is to determine whether turtles can evolve into rabbits and birds,” says Carter. The scientists have identified men in the Active Surveillance program who were initially diagnosed with low-grade disease, but during the close follow-up turned out to have high-grade cancer found on a repeat biopsy, which resulted in radical prostatectomy. Using those pathology specimens, “the low-grade and high-grade components of the cancer within the same prostate will be genetically sequenced to determine how these cancer cells are related,” says Carter.

The scientists hope that by making a “genetic fingerprint” of these tumors, they can answer some key questions, including: Did the low-grade cancer somehow morph into high-grade disease, or did both low- and high-grade disease just happen to spring up together?

Do these high-grade cancers leave some sort of calling card — a genetic marker that could be used to predict whether men have cancers that are actually birds in turtle clothing? The investigators will also look at a control group — low-grade cancer that has remained low-grade, “to determine if there are high-grade markers within these low-grade cancers,” Carter continues. “Lastly, if we find definitive markers of high-grade cancer within low-grade cancer, we will sequence prostate biopsies to determine if disease that we diagnosed as low-grade actually contained high-grade markers.”

This information could help men with a diagnosis of low-grade cancer know whether they will eventually need treatment.

Prostate Biopsy: Can a Robot Make it Better?

Misop Han, M.D., The David Hall McConnell Professor of Urology, believes that prostate biopsies don’t provide enough information. “A typical transrectal ultrasound (TRUS)-guided biopsy has significant limitations,” he explains, because the probe is handled by human hand.” In new research funded by the Patrick C. Walsh Prostate Cancer Research Fund, he and his co-investigators, robotics expert Dan Stoianovici and epidemiologist Bruce Trocik, plan to improve TRUS-guided prostate biopsy with a novel robotic TRUS manipulator (called a TRUS Robot), “which was developed in our laboratory.”

With robotic guidance, Han believes, the TRUS-guided biopsy will not only be able to provide important information about the precise location of the biopsy cores, but about the stiffness of the prostate. As urologist Patrick Walsh explains, the prostate should feel soft in a digital rectal exam, “like the pad of your thumb. But if there is cancer, it feels harder,” more like a knuckle. The biopsy needle can’t feel; but Han hopes to fix this. “With the TRUS Robot, we are incorporating a new imaging modality, ultrasound elastography, which can detect the relative stiffness of the prostate. With elastography guidance, regions of elevated relative stiffness will also be included in the biopsy plan,” to make the urologist aware of any “trouble spots” that may need further investigation.

Targeting Prostate Cancer Cells That Hibernate

When cancer escapes the prostate, some cells go to the bone marrow, where they are alive but dormant. “These sleeping cells are resistant to conventional therapy,” says scientist Sushant Kachhap, Ph.D., which means that if they wake up and cancer begins to grow outside the prostate, “there are very few therapeutic options.”

The dormancy seems to have a protective effect — think of Sleeping Beauty, who managed to sleep for 100 years and hadn’t aged a day when the prince woke her up. Kachhap is intrigued by these hibernating prostate cancer cells. What makes them sleep? What wakes them up?

“While we know a great deal about how cancer grows, very little is known about the biology of prostate cancer dormancy,” he says. “This makes targeting these dormant cells a challenge, but also extremely important.” Kachhap believes that the ability to become dormant is acquired “very early in the process of metastasis, when prostate cancer cells leave the prostate and enter the bloodstream.”

The dormancy seems to have a protective effect — think of Sleeping Beauty, who managed to sleep for 100 years and hadn’t aged a day when the prince woke her up. “Normally, when cells break off from the parent organ, they die due to a mechanism called anoikis. But detached prostate cancer cells survive by signaling a process called autophagy, where parts of the cell are broken down and the energy is used for survival.” In research supported by the Patrick C. Walsh Prostate Cancer Research Fund, Kachhap will use cell and animal models to investigate what triggers dormancy in prostate cancer cells — whether it’s caused by breaking off from the main tumor, or by autophagy, or something else. “Moving forward, we will test whether inhibiting autophagy can lead to death of dormant prostate cancer cells. We believe that this work can lead to new strategies for targeting dormant prostate cancer cells, and inhibiting metastatic cancer.”

Who Can Benefit from Drugs That Stop Cancer Cells From Repairing Themselves?

Anthony Leung, Ph.D., an RNA biologist, is interested in drugs that inhibit PARP. PARP — which stands for poly(ADP-ribose) polymerase — inhibitors have shown promise in treating ovarian, breast, and prostate cancers. “These drugs are designed to target cancers that already have defects in their ability to repair DNA, and rely on remnant repair pathways for survival,” he says. “These remnant pathways are mediated by PARP and other enzymes.”

PARP inhibitors have shown promise in treating cancers that have lost both copies of the BRCA1 or BRCA2 genes, which are responsible for repairing DNA. But despite early promise, PARP inhibitors have not had the hoped-for success in clinical trials.

Leung believes that targeting enzymes other than PARP may be the key. “PARP isn’t the only one. The cancer cells have some backup enzymes,” he says. “We could inhibit a different enzyme that is important for the survival of this cancer cell.”

Leung will use a mouse model of prostate cancer to test whether targeting PARP can slow the progression of the disease. In his mouse model, prostate cancer cells contain a naturally occurring genetic mutation that makes the PARP enzyme less effective. By testing PARP inhibitors on the mouse model, Leung hopes to identify the enzyme that is needed for the cancer cell to survive.

Leung’s research into the PARP enzyme may lead to new strategies for treating prostate cancer. “We are at the very beginning of this work,” he says. “The PARP enzyme is a target of interest, but there are many other enzymes that could be targeted.”

It’s been going strong for a decade now. 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 help us save lives with better ways to treat and prevent it. Applications are reviewed by a Scientific Advisory Board composed of noted Hopkins scientists and lay members. 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, which wouldn’t be possible without your help.
To scientists, these marks are the equivalent of signposts, and “we predict that people who will respond to these drugs will have a distinctive set of protein marks.”

With support from the Patrick C. Walsh Prostate Cancer Research Fund, Leung hopes to develop such a tool, along with Hopkins co-investigators Ken Pienta, H. Ballentine Carter, and Robert Cole; and Phillip Sharp, of the Koch Institute for Integrative Cancer Research at the Massachusetts Institute of Technology. “As its name implies, a PARP inhibitor stops the PARP enzyme from working,” explains Leung. “PARP works by putting a specific mark on proteins in cancer cells, the abnormal activity of PARP even adds marks to proteins that are normally unmarked.” To scientists looking at proteins, such marks are the equivalent of signposts, and “we predict that people who will respond to these drugs will have a distinctive set of protein marks.” Thus, the ability to identify these protein marks may likely be the key to predict which patients will respond well to PARP-inhibiting drugs. Recently, our lab published a highly sensitive method to identify such protein marks. We are now geared to apply our method to a panel of prostate cancer cell lines. “Some of these cancer cells are killed by PARP inhibitors, and some are not. “Using these data, we will be able to identify which protein marks can distinguish responders from non-responders.”

Leung hopes this work will identify a biomarker that can be used in a blood test to help determine which men will benefit from PARP-blocking drugs.

Ultra-Precise Targeting and Killing of Metastatic Prostate Cancer

Radiopharmaceutical therapy is an ultra-precise way of targeting and treating cancer cells. Scientist Sangenta Ray, Ph.D., is integrating molecular PET and CT imaging, “with the ultimate goal of tumor-specific treatment of castration-resistant prostate cancer.”

What will happen next in cancer cells is akin to lighting up a gun’s target with a laser sight – making them much easier to see and kill.

With support from the Patrick C. Walsh Prostate Cancer Research Fund, Ray and co-investigator Martin Pomper are developing a very specific, low-molecular-weight “therapeutic” agent. Therapeutic is another new word you may be seeing more of; it’s a combination of therapeutics and diagnostics, and it’s a key term in the growing field of personalized medicine. Ray’s goal is “to treat multiple sites of disease simultaneously, minimizing damage to adjacent normal tissue, and to treat metastases at an earlier point, when the volume of disease is lower,” she says. “Currently, this is challenging to achieve with standard external-beam therapy.” Ray is aiming to develop an imaging agent that targets a molecule on the surface of prostate cancer cells, the same one that’s also on healthy cells with functional DNA repair.” What will happen next in cancer cells is akin to lighting up a gun’s target with a laser sight – making them much easier to see and kill.

Based on our preliminary studies, the underlying hypothesis is that the low-molecular-weight agents can be optimized to demonstrate superior tumor penetration and lower toxicity to normal tissues, particularly the kidneys, and to provide greater therapeutic efficacy than currently available treatments.

Ultra-Precise Targeting and Killing of Metastatic Prostate Cancer

Ray and colleagues are conducting innovative studies to determine precisely how HMGA1 causes changes to the nucleus and the cell membrane, and how it can be used to predict which patients will behave aggressively in prostate cancer. They will also uncover the genes and pathways that are turned on by the HMGA1 switch to transform normal prostate cells into invasive cancer cells. Further, they will investigate how patients respond to PARP inhibitors and biomarkers.

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Study the Molecular Switches for Metastasis

You may soon be hearing more about a player called HMGA1. A tiny thing, it is nonetheless crucial for rapid growth and development before birth. Normally, it is switched off or silenced in our cells after birth, but becomes abnormally flipped back on in aggressive cancer cells. During fetal development, it helps to maintain the structure and function of the cell’s nucleus; in “the command post that houses our genetic material and directs the behavior and function of our bodies.” Much like a quarterback on a football team, the nucleus tells the cell either to remain in place or move, or to progress into a more specialized position.” explains molecular biologist Linda Resar, M.D. “The nucleus also dictates whether a cell will grow and divide, or remain quiescent.”

In work supported by the Patrick C. Walsh Prostate Cancer Research Fund, Resar and co-investigators Robert Velliri and Karen Reddy are studying HMGA1 in prostate cancer. Resar’s laboratory discovered that HMGA1 transforms normal cells into aggressive cancer cells. “Moreover, HMGA1 is a marker of poor outcomes for patients with diverse tumors,” she says. “HMGA1 is present in high levels in aggressive prostate cancers, and it drives tumor cell invasion and aggressive behavior in animal models of cancer.” Resar discovered that HMGA1 functions as a key molecular switch that cancer cells need to grow rapidly and spread. “Our preliminary studies suggest that HMGA1 alters nuclear shape and function to flip on genes that enable prostate cancer cells to leave their primary site, invade and metastasize.”

Resar’s laboratory discovered that HMGA1 transforms normal cells into aggressive cancer cells.

Prostate Cancer Screening: Is There a Better Way?

Half of the men will, like millions of American men, undergo standard PSA testing and receive a biopsy if the PSA is elevated. The other men will get the same PSA testing, and then will undergo mpMRI, a painless, non-invasive procedure, before biopsy. “For those undergoing MRI and then biopsy, biopsy will be performed with MRI-ultrasound fusion technology.” In addition, the group will assess the usefulness of biomarkers that recently have come into clinical practice, and determine the cost-effectiveness of the two screening strategies. “The results of this trial will have immediate implications as to how we screen men for prostate cancer.”

Improving Control of Cancer in the Bones

One of the worst features of advanced prostate cancer is bone metastasis. A new agent called Radium-223 dichloride has shown success here; it is an alpha particle-emitting radionuclide that is incorporated in the bone material. It emits highly toxic alpha particles that kill cancer in the bone; however, it has a very short range. In fact, it only kills the cells directly next to it in the bone. In research supported by the Patrick C. Walsh Prostate Cancer Research Fund, nuclear medicine scientist Daniel Thorn, Ph.D., with co-investigator Ryan Riddle, hopes to find out exactly how Radium-223 works at sites of bone metastasis. “In initial studies, we have developed small animal models of prostate cancer metastasis in the bone, and we are
THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND

Creating a Vaccine Against Prostate Cancer

Trying to work around prostate cancer’s impressive ability to defend itself is like a molecular game of chess. The technology is there; the key is to figure out the best strategy. For example, Viscidi says, “cancers have recently been shown to block immune responses by expressing inhibitory proteins.” Two of these proteins are CTLA4 and TIM-3. But in a counter move, scientists have developed antibodies that block these proteins. Will it strengthen the immune system of mice. What the team is doing, trying to work around prostate cancer’s impressive ability to defend itself, is like a molecular game of chess. The technology is there; the key is to figure out the best strategy.

Bivalacqua says. “This new molecular-based test will help us identify bladder cancer patients who will benefit the most from chemotherapy before radical cystectomy.”

More Brady Urology Cancer News

The key is frailty, he says. “We know that age alone does not tell us how a patient will do after surgery. Some patients are young but frail, while others are older with great physical reserve.” Bivalacqua says this is an objective measure that does not tell us how a patient will do after surgery. Some patients are young but frail, while others are older with great physical reserve.

Who Could Benefit From Platinum-Based Chemotherapy?

Some patients with muscle-invasive bladder cancer can benefit from systemic chemotherapy before they undergo radical cystectomy. Chemotherapy administered before the operation is called neoadjuvant chemotherapy, and its proven benefits include improved overall survival and a lower risk of having a recurrence of bladder cancer. However, “it still is not widely administered,” says Trinity Bivalacqua, M.D. “It does not tell us how a patient will do after surgery. Some patients are young but frail, while others are older with great physical reserve.”

Who Could Benefit From Platinum-Based Chemotherapy?

The standard of care for patients with muscle-invasive bladder cancer is radical cystectomy, the surgical removal of the bladder. However, Dr. Bivalacqua says, “This is a major operation, with a significant risk of complications and potentially, even death.” Radical cystectomy is not the ideal treatment for everyone. Dr. Bivalacqua says, “We know that age alone does not tell us how a patient will do after surgery. Some patients are young but frail, while others are older with great physical reserve.”

Bladder Cancer Surgery: Who is Likely to Have Complications?

Dr. Bivalacqua says, “We hypothesize that glycoproteins specifically altered in aggressive prostate cancer cells can be released to urine and used as biomarkers.” They also plan to use high-resolution, noninvasive nuclear imaging to show where the radionuclide is deposited. “This may provide insight into improving the techniques we use high-resolution, noninvasive nuclear imaging to show where the radionuclide is deposited. “This may provide insight into improving the techniques we use to personalize the application of prostate cancer treatment.”

who can safely avoid surgery? Although several institutions have studied surveillance, these studies have mainly been retrospective, after-the-fact. “Few institutions have followed their patients to make sure that active surveillance is a safe option for them,” says Pierorazio. Six years ago, he and urologist Mohammad Alfall, M.D., the Mohamed Alfall, M.D. "at the University of Urology, Pathology, and Oncology, who is a pioneer in active surveillance and a leader in the field of active surveillance and a leader in the field of active surveillance.”

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How is the kidney tumor? If it's small, less than 4 centimeters, “upwards of 30 percent are benign, not even cancer,” says Phillip Pierorazio, M.D. "at the University of Urology, Pathology, and Oncology, who is a pioneer in active surveillance and a leader in the field of active surveillance.”

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“bladder cancer surgery: who is likely to have complications?" Bivalacqua says. “We know that age alone does not tell us how a patient will do after surgery. Some patients are young but frail, while others are older with great physical reserve.” Bivalacqua says this is an objective measure that does not tell us how a patient will do after surgery. Some patients are young but frail, while others are older with great physical reserve.
Is a Kidney Tumor Benign? This Not-So-New Test Can Tell

More cases of kidney cancer are being diagnosed now than ever before, in large part due to an increase in the use of cross-sectional imaging techniques such as CT and MRI. But many of these cancers are slow-growing and benign, and may not ever need to be treated, says urologist Michael Gorin, M.D. The problem, he adds, is that “in standard imaging, it’s hard to tell whether a tumor is aggressive or not. Some tumors, particularly benign oncocytomas and hybrid oncocytic/chromophobe tumors (HOCTs) are unique in that they are composed of cells with numerous densely-packed mitochondria, the ‘battery’ that makes the cell’s energy...”

“...This test offers the potential of sparing a significant number of patients an unneeded invasive surgical procedure.”

In the field of nuclear medicine, radioactive substances that are administered intravenously can be detected on a scan to measure how well or poorly an organ is functioning. One such imaging agent has a difficult name: 99mTc-sestamibi. “It is widely available, often used for heart imaging and to show parathyroid adenomas,” says Pierorazio. The investigators plan on confirming this with a larger study. Besides Gorin, Allaf, and Pierorazio, authors included Mark Ball, Christian Pavlovich Jonathan Epstein and Alex Baras.

In related news: Better Diagnosis of Kidney Tumors

Risk-stratification is like “picking out the bad apples and leaving the good behind,” says Brady chief resident Mark Ball, M.D. Because so many tumors are benign, anyone with a kidney tumor are imaged prior to surgery. “This allowed us to compare the results of the imaging test to the gold standard of surgical pathology,” says Gorin. In this study, eight of 50 patients were diagnosed with benign oncocytomas or HOCT at the time of surgery. 99mTc-sestamibi and SPECT/CT imaging correctly identified five of six oncocytomas and two out of two HOCTs, resulting in an overall sensitivity of nearly 88 percent. “Using this technology, we can be very certain that patients with a ‘hot’ tumor have a benign mass,” states Allaf. In addition, only two tumors were falsely positive on the imaging test. “Based on these findings, 99mTc-sestamibi SPECT/CT appears to be an excellent test for the preoperative identification of benign renal tumors and offers the potential of sparing a significant number of patients an unneeded invasive surgical procedure,” says Pierorazio. The investigators plan on confirming this with a larger study. Besides Gorin, Allaf, and Pierorazio, authors included Mark Ball, Christian Pavlovich Jonathan Epstein and Alex Baras.

In a study led by Ball and recently published in the journal, Urologic Oncology: Seminars and Original Investigations, the investigators studied more than 1,000 patients from five different hospitals and identified factors associated with a higher risk of being cancer. Men were at higher risk of having cancer than women; other risk factors include a tumor size greater than 3 centimeters, and a high nephrometry score (a measure of tumor complexity on CT scan). “Patients with all three risk factors had an 89-percent chance of having cancer,” says urologist Mohamad Allaf, M.D., the study’s senior author, “while patients with none of these risk factors have only a 64-percent chance of having cancer.” Ball adds: “This nomogram can help us do a better job of predicting which patients are more likely to have cancer, but it’s not enough yet. Better tests are still needed to predict which patients can forego surgery, and who needs aggressive treatment.”

In other recent findings, published in The Journal of Urology, the team studied how areas of a kidney tumor may look different (or heterogeneous) under the microscope. “We found that even the most aggressive tumors have areas that look less aggressive under the microscope,” says Ball, who was the study’s lead author. This may mean that biopsies are not that helpful. “Renal mass biopsy is sometimes used before surgery to confirm the diagnosis, but it’s not a perfect test, and our study shows that it can sometimes give false reassurance,” says urologist Phillip Pierorazio, a coauthor of the study.

“Early-stage testis cancer generally affects young, otherwise healthy men, and — if it weren’t such an arduous procedure — RPLND could eliminate the need for a prolonged course of cancer surveillance or the long-term side effects of chemotherapy.”

In a disease that is 99 percent curable and with patients who have little surgical risk due to their young age and good general health, the argument could be made for aggressively treating men with low-stage disease with a minimally-invasive procedure.”

Testis cancer generally affects young, otherwise healthy men, and — if it weren’t such an arduous procedure — RPLND could eliminate the need for a prolonged course of cancer surveillance or the long-term side effects of chemotherapy. “In a disease that is 99 percent curable and with patients who have little surgical risk due to their young age and good general health, the argument could be made for aggressively treating men with low-stage disease with a minimally-invasive procedure.”

From left, Allaf, Harris, and Pierorazio: New procedure is “technically challenging,” but is a better, minimally invasive cancer operation. Note: Pierorazio sports a mustache grown in “Movember” to support testicular cancer research and treatment.
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