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It has been called the “invisible” cancer, because bladder cancer research has been desperately underfunded. With the help of two philanthropists, Stephanie Cooper Greenberg and Erwin L. Greenberg, we created the Greenberg Bladder Cancer Institute, the first of its kind in the world. Now after an international search, we have the Institute’s first Director, David McConkey. We have so much exciting news about our bladder cancer research and treatment that we made this our cover story. In related stories (see Page 20), you’ll read about our pioneering work on engineering a new bladder; on who will benefit from chemotherapy before surgery; and more.

We remain at the forefront of prostate cancer research and treatment, as well. In a new study (see Page 4), our scientists show that the current recommended cutoff for prostate cancer at age 75 is missing cancer that really needs to be treated. We discuss new findings that some high-grade PIN is actually established cancer (see Page 12); that if you quit smoking, you are less likely to die of prostate cancer (see Page 6); and we continue our reporting of how prostate cancer is different in African American men (see Pages 7 and 8). We also highlight the exciting multidisciplinary research you have helped make possible with this year’s Patrick C. Walsh Prostate Cancer Research Fund winners.

We bring you the latest news in kidney and testicular cancer (see Page 22-23), including the use of new immune-boosting drugs to treat metastatic kidney tumors. As always, we have more happening than we have room in these pages to tell you about, and as always, our momentum brings us great hope and excitement for the future.

Best wishes,

Alan W. Partin, M.D., Ph.D.
The Jakurski Family Director
Urologist-in-Chief
Professor of Urology
The James Buchanan Brady Urological Institute
Never has there been so much hope and excitement in the field of bladder cancer research and treatment, and the Greenberg Institute is right at the forefront. Gene-based approaches are creating smarter, more targeted treatments. New immunotherapy drugs are curing cancers that even a few years ago proved deadly. Brady scientists stand at the brink of a revolution in restorative surgery — creating entirely new replacement bladders out of a patient’s own tissue and stem cells. And we are excited to tell you that after an international search, the Institute has its first Director: David McConkey, Ph.D.

So many advances, and so much to look forward to — not bad at all for one of the world’s lowest-funded and most notoriously under-investigated diseases.

In fact, it was this great need to find scientific answers and develop better treatment for what has been called the “invisible cancer” that led Baltimore philanthropists Stephanie Cooper Greenberg and Erwin L. Greenberg last year to commit $15 million, with a $30 million co-investment from The Johns Hopkins University, to start the Greenberg Bladder Cancer Institute — the first of its kind in the world.

McConkey comes to the Brady from the University of Texas M.D. Anderson Cancer Center, where he was the Director of Urological Research and Professor of Urology. “David McConkey is well recognized by his peers as a leading scientist and patient advocate, and is internationally renowned for his research on bladder cancer,” says Trinity Bivalacqua, M.D., Ph.D., Director of Urologic Oncology.

Molecular subtypes: McConkey is part of a group of scientists working together on bladder cancer from around the world. Over the last few years, they have noticed some important similarities between bladder cancer and breast cancer. “We discovered that muscle-invasive bladder cancers can be grouped into subtypes of basal and luminal tumors that resemble the ones found in breast cancers,” says McConkey. These cancers behave differently: “Like their breast cancer counterparts, basal bladder cancers are more aggressive, and are associated with early metastasis and death in patients who do not receive cisplatin-based chemotherapy.” But there is good news for people with these cancers: “We discovered that patients with basal cancers who receive neoadjuvant chemotherapy actually have excellent long-term outcomes.” McConkey and colleagues recently published these findings in European Urology. If the results of their study are confirmed, “this should prompt clinicians to be more aggressive in offering presurgical chemotherapy to all patients who have these potentially lethal basal bladder cancers.”

Gene-targeted treatment and immunotherapy: The bladder has a unique advantage when it comes to cancer treatment: “The organ is confined,” says McConkey, “and we can exploit that.” For years now, urologists have been using BCG (bacilli Calmette-Guerin), a form of bacteria used in the tuberculosis vaccine, to treat some noninvasive bladder cancers. BCG, delivered directly into the bladder through a catheter, stimulates the immune system to fight off cancer cells. Sometimes it is used in combination with another immunotherapy drug called interferon alpha 2b. “In many cancers, delivery is a major problem. But we are putting people into long-term remission, and there are many possibilities for gene editing and gene transfer,” fixing a mutated gene by switching it with an undamaged one. Bivalacqua, with physician-scientist Colin Dinney, M.D., Chairman of Urology at MD Anderson, is investigating another form of interferon gene therapy using an adenovirus (the virus found in the common cold).

Continued next page »
Exciting new immunotherapy drugs called “checkpoint inhibitors” are achieving results considered miraculous in many forms of advanced cancer. Several newly available drugs target specific proteins that fool the immune system into thinking cancer is not an enemy: when these proteins are blocked, the immune system recognizes tumor cells and attacks them, in many cases causing tumors to melt away. In bladder cancer, however, the optimal genetic warrior drug has not yet been found; McConkey, Bivalacqua, Noah Hahn, M.D., and colleagues at MD Anderson believe a molecule called fibroblast growth factor receptor 3 (FGFR3) is a promising target, and they have received an innovation award from the Bladder Cancer Advocacy Network (BCAN) to study it. “In bladder cancer, lymphocytes — disease-fighting white blood cells — are not able to penetrate the tumors very well,” he says. But blocking FGFR3 may open the door for lymphocytes to elbow their way into bladder tumors and start killing cancer cells.

Better reconstruction: “Tissue engineering is the ultimate in reconstruction,” says McConkey, “and we have a fantastic team assembled by Trinity Bivalacqua” to create a new bladder out of a patient’s own cells. Layering stem cells and similarly plastic cells called progenitor cells around a scaffold, Bivalacqua and Brady colleagues are “doing 3-D chemistry.” Getting these cells to take their proper places on the scaffold has been a huge challenge, “but Trinity solved it.” If this work proves successful, one day instead of crafting a neobladder out of bowel tissue, surgeons will simply remove the old bladder and put in a brand new one.

Raising the profile: Bladder cancer has long ranked near the bottom in research money spent, despite the number of people who have it, says McConkey. “It’s important to get the word out, not just to help support NIH investment in bladder cancer research, but also to help the public understand what a significant health problem it is.” Cigarette smoking is the biggest risk factor, but there is no targeted screening. “Although people with a history of smoking have a much higher risk, many doctors don’t connect those dots right away.” The other part of the low-profile problem is that “people who are diagnosed just don’t want to talk about it,” although that’s changing with the help of BCAN, he adds. Also changing is the momentum in developing new forms of treatment. Until the recent success of checkpoint inhibitors, “pharmaceutical companies weren’t all that interested in developing clinical trials in bladder cancer. Now they are,” and with better surgery and new genetic strategies, “we’re experiencing a perfect storm that is leading to rapid progress.”

Healthy Men Over 75: Don’t Stop PSA Screening

We are living longer, and 75 is not the ripe old age it used to be. But it’s a cutoff age for PSA screening — and this is missing cancer in men who really need to be treated, say Brady investigators. “There is increasing evidence that this age-based approach is significantly flawed,” says Patrick C. Walsh, M.D., University Distinguished Service Professor of Urology.

Walsh is the senior author of a recent Brady study that looked at high-risk prostate cancer in older men. The study’s interdisciplinary group of investigators also includes first authors Jeffrey Tosoian and Ridwan Alam, and Carol Gergis; Amol Narang, Noura Radwan, Scott Robertson, Todd McNutt, Ashley Ross, Danny Song, Theodore Deweese, and Phuoc Tran.

The U.S. Preventive Services Task Force recommends against screening for men over 75. “There’s no question that there has been overtreatment of prostate cancer,” says Tosoian. “However, that is getting better; more men are taking part in active surveillance programs, and we are much better at interpreting PSA and other biomarkers to rule out aggressive disease.”

But PSA can’t be interpreted if a man doesn’t get his PSA tested. Population studies have shown that “men diagnosed at 75 years or older account for 48 percent of metastatic cancers and 53 percent of prostate cancer deaths, despite representing only 26 percent of the overall population,” says Tran, Clinical Director of Radiation Oncology and Molecular Radiation Sciences.

Why are older men more likely to die from prostate cancer? To find out, the team studied 274 men over age 75 who underwent radiation therapy for prostate cancer. “We found that men who underwent PSA testing were significantly less likely to be diagnosed with high-risk prostate cancer, and that men with either no PSA testing or incomplete testing (either a change in PSA was not followed up, or a biopsy was not performed when it was indicated) had more than a three-fold higher risk of having high-risk disease at diagnosis, when adjusted for other clinical risk factors,” says Tran.

Although this was a small study and more research is needed, Walsh says, “we believe that PSA screening should be considered in very healthy older men.”

* Tosoian: Without screening, many older men are likely to die of prostate cancer.
For years, the biggest frustration with the prostate biopsy has been that it is “blind.” That is, although they are guided by ultrasound, urologists doing a biopsy really can’t see whether one area of the prostate looks any different from another — so they do the best they can by trying to sample tissue in a systematic way throughout the gland. The problem with this approach, says urologist H. Ballentine Carter, M.D., the Bernard L. Schwartz Distinguished Professor of Urologic Oncology, is that “we often miss significant prostate cancers. About half of men require a repeat biopsy within five years because of concerns that cancer is hiding there and was simply missed.”

Good news: Biopsy is getting a whole lot smarter with a new approach called multi-parametric MRI (mpMRI)-guided biopsy, also known as fusion or targeted biopsy. mpMRI-guided biopsy uses three different ways of looking at prostate tissue to help determine the presence of cancer, says Carter. “One is the tissue signal intensity upon exposure to a strong magnet. Another is how well water diffuses through the tissues; and the third is how well the contrast material is taken up, and how quickly it washes out of the tissues.” These three parameters are important, he explains, because “compared to normal tissue, prostate cancer is associated with low signal intensity, low water diffusion, and earlier contrast enhancement with faster washout of contrast.”

At Johns Hopkins, radiologists use a grading system (the Prostate Imaging Reporting and Data Systems, or PI-RADS) from 1-5 based on results of the mpMRI to indicate the likelihood that cancer is present. Grade 1-2 means a low suspicion of cancer; grade 3, right in the middle, is “indeterminate suspicion,” and grade 4-5 suggests a high suspicion. “Prostate MRI can be used to assess the probability that cancer is present, and also the probability that a high-grade cancer is present,” says Carter. “But MRI cannot diagnose prostate cancer; only a biopsy can do that.”

The mpMRI lays the groundwork for the biopsy. “During the biopsy, which is done with ultrasound guidance, we overlay the MRI image and the ultrasound image, fusing them together to directly target abnormal regions seen on mpMRI,” says Carter.

Carter and colleagues recently looked at the capability of targeted biopsy vs. traditional biopsy in three groups: men with elevated PSA levels who had never had a biopsy; men newly diagnosed with prostate cancer who met criteria for active surveillance and were undergoing a second biopsy to make sure their disease was low-grade, slow-growing and safe enough not to be immediately treated; and men already enrolled in active surveillance who were undergoing routine follow-up biopsies. Their study was published in the May 2016 issue of European Urology. The results were most striking in the first group of men — those who had never undergone a biopsy before. Targeted biopsy identified higher-grade cancers in 16 percent of these men — cancers that standard biopsy missed.

In the second and third groups, “targeted biopsy identified high-grade disease that had been missed by systematic biopsy in only 4 to 5 percent of individuals,” Carter reports. “Therefore, we believe that image-guided biopsy provides useful information over and above regular biopsy for men with an elevated PSA, but not necessarily for those who meet strict criteria for active surveillance. However, image-guided biopsies could help expand the pool of individuals for whom surveillance would be safe.” And further good news for men on active surveillance: “Among men who had no PI-RADS 3 or higher lesion, there was a 90-percent likelihood of finding no cancer of Gleason score above 6 on biopsy. For those men, frequent biopsies to monitor their cancer while on surveillance may be unnecessary.”

Carter: Targeted biopsy finds higher-grade cancers that standard biopsy has missed.
Studying the Seeds of Metastasis

What makes them dormant, and what makes them start to grow? And what makes them leave the prostate in the first place?

The first step to metastasis is for a few hardy cells to escape the main tumor and enter the bloodstream. These are circulating tumor cells, or CTCs. The bloodstream is a dangerous highway — think of the Autobahn — and not every cancer cell can survive it. But the toughest cancer cells manage to keep up with the traffic, exit the highway, and find a new place to live. These cells become “disseminated tumor cells,” or DTCs.

“Prostate cancer tends to metastasize to lymph nodes and bone marrow,” says oncologist Ken Pienta, M.D., the Donald S. Coffey Professor of Urology and Professor of Oncology and Pharmacology and Molecular Sciences. “These cells can remain dormant for a long time — years or even decades — before they begin to grow large enough to become detectable metastases.”

What makes them dormant, and what makes them start to grow? And what makes them leave the prostate in the first place? “We don’t know at what point during cancer development that these cancer cells escape the prostate and seed sites around the body,” says Pienta, who is the Brady’s Director of Research. He and his team have begun to try to understand the process of CTCs disseminating, and then of DTCs remaining dormant.

To do this, they have collected more than 255 blood and bone marrow samples from men undergoing a prostatectomy. “These samples were distributed throughout the country in a multi-institutional effort to understand how often and in what capacity these CTCs and DTCs could be detected with the most recent technology,” he explains. Of those samples, 45 bone marrow samples were processed in the Pienta Lab with a scanning microscope system that finds single cancer cells that would otherwise go undetected. “We hope to learn which men are at higher risk for recurrence after surgery, and who should have a more aggressive approach to treatment.”

Men Who Quit Smoking Are Less Likely to Die of Prostate Cancer

Here’s another reason not to smoke, and for men it’s a big one: If you smoke, you are more likely to develop aggressive prostate cancer, and to die from it. If you already have prostate cancer and you continue to smoke after your treatment, the prostate cancer is more likely to come back, and you are more likely to die from it.

The good news is that if you stop smoking, your risk of dying of prostate cancer returns to that of someone who has never smoked.

Over time, if you quit smoking, your risk of dying of prostate cancer becomes that of a man who has never smoked.

In exciting work, epidemiologists Miranda Jones, Ph.D., Corinne Joshu, M.P.H., Ph.D., and Elizabeth Platz, Sc.D., M.P.H., have shown this on a large scale. “We knew what was happening in our cohort studies of men who smoked, quit smoking, or never smoked,” says Platz. The team wondered, might there be a similar drop in prostate cancer deaths in entire states where the prevalence of smoking has gone down?

It took 50 years — from 1964, when the first U.S. Surgeon General’s report on Smoking and Health blamed cigarette smoking as a cause of many cancers, to 2014 — before the U.S. Surgeon General officially concluded that smoking also raises the risk of death from prostate cancer. And it has taken years of policy changes — carrot-and-stick strategies such as cigarette taxes, workplace smoking bans, indoor air pollution laws, and offering free or low-cost services to help people stop smoking — but they have worked. Several states “have significantly lowered the number of people who smoke,” Platz says. They looked at four states where the number of smokers has changed significantly: California, Kentucky, Maryland, and Utah.

The team looked at prostate cancer death rates in these states between 1999...
and 2010. “This was fully in the PSA era,” Platz notes, when screening for prostate cancer became more widespread. “We found that as the prevalence of smoking declined in these states, their prostate cancer death rates declined in parallel.” This work was published in Preventing Chronic Disease. How did they know that the drop in deaths was due to men quitting smoking, and not other reasons? They looked at other kinds of deaths, such as “accidents, homicides, and suicides, deaths from external causes that would not be related to smoking, and did not see this pattern,” Platz says. Also important: “these declines in smoking and prostate cancer mortality were evident in black and white men.”

Next, in collaboration with investigators in the Atherosclerosis Risk in Communities study, the team looked at the health of more than 6,600 men, white and black, who started the study when their average age was between 54 and 55. They followed the men’s health from the late 1980s through 2012. They also took into account age, education, body mass index, height, and physical activity. Over an average of nearly 20 years, 84 of the men had died of prostate cancer. “Compared with men who had never smoked, men who were smoking cigarettes at the start of the study had almost twice the risk of dying of prostate cancer in the future,” says Platz. “Men who had quit smoking before the study started, and men who had occasionally smoked pipes or cigars did not have an increased risk of prostate cancer death. Looking more closely at the timing of smoking, men who continued to smoke cigarettes or who quit within 10 years had 1.85 times the risk of death from prostate cancer — but men who quit longer ago did not have an increased risk.” In other words, over time, if you quit smoking, your risk of dying of prostate cancer becomes that of a man who has never smoked. “These patterns were the same in both white and black men.”

Platz worries that the message to “quit smoking” has gotten stale; that we’ve all heard it so much, we tune it out. “But here is a potential strategy to reduce the number of prostate cancer deaths, including in black men — who suffer a disproportionate burden of prostate cancer.” About 17 percent of American men still smoke. “There is more help to quit smoking now than ever, and not dying of prostate cancer is a very good incentive to quit.”

Prostate Cancer Test Results May Differ in African American Men

Much of what we know about prostate cancer comes from studies that primarily involved white men. Brady scientists have led the way in discovering that the disease is not the same in African American men. (In related news: Cancer makes less PSA in African American men — please see Page 8.)

It turns out that there are different genetic alterations in prostate cancer based on race. Several years ago, Brady scientists discovered that a tumor suppressor gene (which helps fight cancer) called PTEN is commonly lost in prostate cancer; moreover, when it is knocked out, the cancer tends to be more deadly. So striking was this finding that pathologist Tamara Lotan, M.D., and colleagues recently developed a simple, inexpensive test to look for the absence of PTEN in prostate tumors. To validate the test’s accuracy, Lotan’s lab teamed up with investigators from the Harvard School of Public Health to show in a large, population-based study that PTEN loss is associated with death from prostate cancer; their results were published in 2016 in the Journal of the National Cancer Institute (JNCI).

“This test is available at the Johns Hopkins Hospital and is being used in selected prostate biopsies to help predict how aggressively the tumor is likely to behave,” says Lotan. However: “It is important to note that most studies of PTEN have occurred in white men of European ancestry,” Lotan says. “Though African-American men have a higher risk of death from prostate cancer, it is unknown whether they might have a higher rate of some of the same genetic changes that have been linked to aggressive disease in white men.”

It is important to note that most studies of PTEN have occurred in white men of European ancestry.

To address this question, Lotan and Brady resident Jeff Tosolian, M.D., M.P.H., compared the frequency of PTEN loss in African-American men and white men who underwent radical prostatectomy. They found that PTEN was lost significantly less often in African-American men — in 18 percent, as compared to 34 percent of white men. However, “similar to what we have seen in white men, the African American men who had PTEN loss had a risk of developing metastatic disease that was nearly four times higher than that of men who did not have PTEN loss.”

Lotan suspects that different genetic aberrations — the loss of another protective gene, perhaps — may be involved in African American men. “Additional research is needed to identify these alterations, and to develop interventions aimed at each tumor’s genetic basis,” she notes, “leading us into an era of precision medicine.”
Mast Cells Linked to Risk of Cancer Recurrence

Men who had more mast cells in their tumor were less likely to have a return of cancer

Is it possible that an allergic response could be good for you? Research led by scientist Karen Sfanos, Ph.D., suggests that in men with prostate cancer, the answer is yes: the key seems to be mast cells.

Mast cells are complicated. A type of immune cell, they do good things — help fight off pathogens and heal wounds — yet also can lead to severe allergic reactions. It's not often that mast cells and prostate cancer are spoken of together; that will likely change, thanks to the work by Sfanos and a multidisciplinary Hopkins team. “We have discovered that mast cells may be linked to prostate cancer recurrence,” says Sfanos, who has been working for several years with a team of Brady scientists to figure out the immune system’s role in prostate cancer.

“Mast cells are primed to respond quickly whenever they detect something harmful, such as an allergen” (a substance that causes an allergic reaction), Sfanos explains. “They can release factors that lead to chronic inflammation and tissue remodeling; both of these are also known to be involved in the development of many types of cancer.”

Is there any significance to the number of mast cells found in cancerous prostate tissue? A recent study conducted by Pathobiology graduate student in Sfanos’ laboratory, aimed to find out. Helping to answer this question were epidemiologist Elizabeth Platz, Sc.D., M.P.H., and pathologist Angelo De Marzo, M.D., Ph.D., who have developed a unique sample set of tissues from men who underwent radical prostatectomy at Hopkins; some of these men experienced recurrence of cancer, and some remained cancer-free. Hopkins pathologists Toby Cornish, M.D., Ph.D., and Nathan Cuka, M.D., also collaborated, designing novel image analysis software that counted the mast cells in each patient’s cancer tissues; other investigators included Ibrahim Kulaç, M.D. and John Barber.

“Somewhat surprisingly, we discovered that high mast cell numbers were inversely associated with prostate cancer recurrence,” says Sfanos. “Very low numbers of mast cells indicated that the cancer was more likely to come back.”

Same PSA, But Not the Same Cancer

In prostate cancer, personalized medicine may be life-saving. “As we learn more about prostate cancer, we are beginning to see that not all ethnic groups are the same,” says Jonathan Epstein, M.D., the Rose-Lee and Keith Reinhard Professor in Urologic Pathology.

Prostate cancer in African American men makes less PSA than it does in Caucasian men

For example: In important new studies, Epstein and colleagues have discovered that prostate cancer in African American men makes less PSA than it does in Caucasian men. This work suggests that in African American men, low-grade prostate cancer (a Gleason score of 3+3=6, or Grade Group 1) may not be as slow-growing as it is in Caucasian men.

“Active surveillance is often recommended for men with low-grade prostate cancer,” says Epstein. “However, the criteria for choosing who the best candidates for active surveillance have been based primarily on studies of Caucasian men.” But in several studies, Epstein and colleagues have been working to add more specific data to the knowledge base. They found that the current criteria for active surveillance “do not work as well in African American men compared to Caucasian men.” Then they demonstrated “that among men with the same volume of low-grade cancer, despite larger overall prostates, African American men had the same PSA.”

They explained this finding by showing that cancer in African American men makes less PSA than it does in Caucasian men. “PSA Density (the PSA score divided by the volume of the prostate, as determined by ultrasound) was about 20 percent lower in African American compared to Caucasian men — even though tumor volume was the same,” Epstein continues. “This finding could be a factor in why current active surveillance criteria in African American men are not as accurate as those for Caucasians.” Epstein suspects that to account for this disparity, the threshold for PSA density will need to be made lower for African American men who want to take part in active surveillance, “with the hope that this will allow us to predict more accurately which African American men will be good candidates for active surveillance.”

Their most recent work was published in the Journal of Urology.
If you have breast, colon, ovarian, or pancreatic cancer in your family, you may be at risk for the most aggressive kind of prostate cancer. This is important news, because for years scientists didn’t make the connection between prostate cancer and other cancers that run in families.

But now, thanks to new work by William Isaacs, Ph.D., The William Thomas Gerrard, Mario Anthony Duhon, Jennifer and John Chalsty Professor in Urology, and colleagues, and several other research groups around the world, we know that there is a short list, a genetic “who’s who” of very bad genes that appear in lethal prostate cancers; these mutated genes are also involved in the worst cancers of the breast, colon, ovaries, and pancreas. They can be inherited by men and women.

The job description for these genes is “DNA damage repair,” and normally, they are supposed to protect the body against the very genetic mistakes that can lead to cancer. Imagine a car factory where someone in charge of quality control breaks his eyeglasses: He misses delicate mistakes in the machinery he’s supposed to inspect; those faulty parts then get put into bigger sections, and before you know it, a defective engine is on its way out the door.

If you have slow-growing prostate cancer, chances are that you do not have one of these damaged genes. In fact, “in many studies of men with less aggressive disease, we have been unable to detect genes linked to lethal prostate cancer,” Isaacs says. He should know; he has identified many genetic variants called SNPs that raise a man’s risk of getting prostate cancer. But these bad stretches of DNA just raise the risk by a very small amount, and just because a man inherits one of them doesn’t necessarily mean that he will get prostate cancer, or that it will be the aggressive kind that really needs to be treated.

In the first study of its kind, Isaacs and colleagues including Jianfeng Xu at NorthShore Research Institute in Chicago recently completed a detailed genetic analysis of 96 men who died of prostate cancer at an early age – younger than 65. “We sequenced all regions on each chromosome that code for proteins,” Isaacs explains. “Surprisingly, we found that more than 20 percent of these patients carry inherited mutations which inactivate a class of genes responsible for repairing damaged DNA.” This is a huge percentage. “This compares to a rate of around 3 percent in men selected for positive family history only. Other recent studies by Stand up to Cancer investigators are finding similar results.”

“Family history is a powerful tool, but we need to better characterize what kind of family history is most meaningful.”

Two of these genetic culprits are BRCA1 and BRCA2; as genes go, they are most famous for their role in inherited breast and ovarian cancer. Others are ATM, PALB2, PMS2, and MSH2, “which typically are associated with breast, pancreatic and colon cancer. “We found the highest frequency of mutations in BRCA2,” says Isaacs. “Studies are under way worldwide to more fully characterize the role of this heretofore breast cancer gene in inherited prostate cancer. Family history is a powerful tool, but we need to better characterize what kind of family history is most meaningful. While much work remains to be done to fully understand these results, we are very excited about these new findings and how they may translate into better ways to identify a man’s risk for aggressive prostate cancer before the cancer even begins.”
At Last, a Mouse Model for the Worst Prostate Cancer in Men

Cancer evolves, and as it changes it becomes more aggressive. Eventually it develops the ability to travel far away from where it started, and invade new territory. This is a remarkably complex achievement; in fact, Brady scientist Don Coffey, Ph.D., once explained it this way: “For the cancer cell to be able to leave the primary tumor and move to distant sites is the equivalent of this building we are in getting up and walking.”

And yet, this is what happens when prostate cancer becomes advanced, and scientists worldwide are working hard to find ways to prevent or stop this process. They may be one step closer now.

“One of the most important ways to study prostate and other cancers is to develop new experimental models using mice,” says Angelo M. De Marzo, M.D., Ph.D., Professor of Pathology, Oncology and Urology. “Unfortunately, in prostate cancer most existing mouse models either do not use genes that are known to be relevant in the human disease, do not resemble human disease in terms of how the cancer cells look to the pathologist and what genes they express, or do not produce metastases as seen in humans.”

Scientists can’t safely test possible new cures without an animal model, and not having a model for the very worst kind of prostate cancer has limited what they could do to help the men who need it most.

Now, thanks to recent work — a project that began with funding from the Patrick C. Walsh Prostate Cancer Research Fund — there is such a model: a new mouse, developed in the laboratory of developmental biologist Charles J. Bieberich Ph.D., from the University of Maryland Baltimore County in collaboration with De Marzo. The team, including Hopkins scientists Gretchen Hubbard, Ph.D. (formerly a graduate student with Bieberich), and Vasan Yegnasubramanian M.D. Ph.D., and Peter Nelson, M.D., from the University of Washington, found that they could set off the process of widespread metastasis in a mouse by combining mutations in two genes that are commonly changed in human prostate cancer, MYC and PTEN.

“Interestingly,” De Marzo notes, “alteration of either one of these genes alone led to the development of small, relatively indolent prostate cancers that did not progress over time.” But William B. Isaacs, Ph.D., has shown in previous work that when both of these genes are mutated in human prostate cancer tissues, there is “a very high chance for the cancer to be aggressive and to become fatal. Thus, there is a tight concordance between what we have learned in humans suggesting which genes might be important for aggressive disease, and the new mouse data showing that indeed, this is the case.” Because the new mouse has both genes altered, scientists who use this model can study metastasis in depth, and look at different strategies for stopping it at various stages as the cancer progresses.

The next step will be to focus on making the mouse model easier to use, “so it can be widely employed by many researchers for testing of promising new treatments.” Others involved in the study include Laura Mutton, May Khalili, Ryan McMullin, Jessica Hicks, Daniella Bianchi-Frias, Lucas Horn, Ibrahim Kulac, and Michael Moubarek.

Is Cancer Aggressive? Soon, You May Take a Urine Test to Find Out

“Oh-diagnosis and over-treatment of indolent prostate cancer is a significant health issue,” says Alan Partin, M.D., Ph.D., the Jakurski Family Director, Urologist-in-Chief and Professor of Urology. “With PSA screening, prostate cancers are diagnosed at an earlier stage, but most tumors have a low risk of progression.” A new urine test may be of help here: Partin was part of a multicenter team that validated the test; their results were published in JAMA Oncology.

To validate the test, Partin and investigators at 22 hospitals in the U.S. compared the prognostic score of the test, called ExoIntelliScore Prostate, with biopsy results in more than 1,000 men. They took into account variables such as PSA score, age, race, and a family history of prostate cancer. “We found that the test was able to discriminate high-grade (Gleason score 7 or greater) cancer from low-grade Gleason 6 cancer and benign disease,” says Partin, “and it improves identification of patients with higher-grade prostate cancer among men with elevated PSA.”
Biomarkers to Predict Aggressive Cancer

Robert Veltri, Ph.D., has developed two new “high-throughput” tools aimed at identifying aggressive prostate cancer and predicting prostate cancer’s progression even when the disease is in the early stages. “The biomarkers development tool is a combination of tissue microarray and multiple tissue immunoblotting.” Using tissue samples from men who have undergone radical prostatectomy, “with this tool, we developed a panel of six biomarkers that could predict aggressive prostate cancer.” And looking at biopsies from men in active surveillance, “we could identify potentially aggressive cancer requiring immediate treatment.” This research was published in Cancer Epidemiology, Biomarkers & Prevention.

In other work: If two pathologists were looking at the same prostate tissue samples, one might see cancer and another one might not. “The diagnosis is relatively subjective,” says Veltri. To help with accurate analysis, Veltri’s lab developed a computer program “that can accurately and automatically quantify the morphometric changes of hundreds to thousands of nuclei within the cancer area. Our results have showed its potential use not only in the improvement of diagnosis, but also in the prediction of aggressiveness of prostate cancer.”

A “Sweeter” PSA Test

Looking for a small chemical change — the addition of a form of sugar to PSA molecules — makes it easier for scientists to tell if a man has aggressive cancer.

“Glycosylation means attaching sugar; it is a common modification of proteins that is involved in many cellular functions,” says Daniel W. Chan, Ph.D., who directs the Clinical Chemistry Division and the Center for Biomarker Discovery, and co-directs the Pathology Core Lab. “It also happens in cancer.” Studies have shown that abnormal glycosylations occur during the series of molecular changes that lead to cancer.

PSA is a “glycoprotein,” meaning that it has sugar attached to it at the molecular level. “In this study, we analyzed blood samples from men with prostate cancer. We measured levels of glycoproteins, and of molecules with a form of sugar called fucose added to them, and then checked them against the Gleason score of the prostate tumor. We found that the fucosylated PSA was elevated and correlated with tumor Gleason scores.” In looking at cancers with a Gleason score greater than 6, “both fucosylated PSA and the ratio of fucosylated PSA were better at predicting aggressive cancer than standard PSA. Our data suggested that fucosylated PSA has the potential to be used as a biomarker to differentiate aggressive from non-aggressive prostate cancers.” This work was funded by the National Cancer Institute, and was published in Theranostics.

End-of-Radiation PSA Helps Predict the Success of Treatment

How well did the radiation treatment work? Radiation oncologists Phuoc Tran, M.D., Ph.D., and Theodore DeWeese, M.D., believe measuring a man’s PSA at the end of treatment may provide a strong clue. “Emerging literature suggests that the PSA response to androgen deprivation therapy (ADT) before radiation may help identify men with disease that is more aggressive,” he says. “Similarly, in men undergoing definitive radiation for localized prostate cancer, the PSA response at the end of treatment may serve as a helpful biomarker.”

This end-of-radiation (EOR) PSA measurement may turn out to be a more helpful marker for guiding treatment strategies than the PSA level before radiation, Tran continues, “and may also be applicable to men undergoing definitive radiation alone. At our institution, it has been the standard practice to obtain an EOR PSA during the last week of treatment. This was instituted by Ted DeWeese when he first began his practice.” Tran and colleagues including DeWeese, Danny Song, M.D., Curtiland Deville, M.D., Stephen Greco, M.D., and Amol Narang, M.D., recently examined the value of the EOR PSA in a group of nearly 700 men with long-term follow-up, average of 11 years, after being treated at Hopkins with definitive radiation for prostate cancer.

“We found that the PSA level during the last week of radiation can predict survival in patients undergoing radiation therapy for prostate cancer,” Tran says. Men who had a detectable EOR PSA after definitive radiation for localized prostate cancer had poorer prognoses. “Notably, men with intermediate- or high-risk disease who underwent neoadjuvant-concurrent ADT who achieved an undetectable EOR PSA level were more likely to live longer and not die of their prostate cancer.”

More studies are needed to validate these results, and to investigate the potential use of the EOR PSA in determining the best treatment for men with localized prostate cancer.
Some High-Grade PIN Is Actually Cancer

Many areas of high-grade PIN are not cancer precursors at all. Instead, “these PIN lesions actually reflect the growth of established cancer into prostate ducts.”

If you’ve ever had a prostate biopsy, you may have encountered the words, “isolated high-grade PIN.” PIN stands for “prostatic intraepithelial neoplasia,” and if you have it, you’re not alone: an estimated 50,000 to 70,000 men are told that their biopsy shows this finding.

Now, what is it? That’s a good question, and the answer has just changed. “For many years, we thought high-grade PIN represented a precursor of prostate cancer,” says William G. Nelson, M.D., Ph.D., the Marion I. Knott Director and Professor of Oncology and Director of the Sidney Kimmel Comprehensive Cancer Center. “Thus, a diagnosis of high-grade PIN was unsettling for both the patient and the physician.” Just to make sure cancer wasn’t there, “often men with high-grade PIN were subjected to a second biopsy, and some of the men were indeed found to have cancer.”

Because nobody really knew what PIN was, and with the hope that it might be reversible, over the last decade several clinical trials were undertaken to see “whether PIN could be intercepted and prevented from progressing to cancer.” Scientists, including Nelson, studied many promising foods and vitamins that are in foods, like “green tea catechins, lycopene from tomatoes and other fruits and vegetables, selenium, vitamins, hormones, and drugs,” Nelson adds.

“Unfortunately none of the trials succeeded: the numbers of men ultimately found to have prostate cancer were unaffected by any intervention.”

New research sheds light on why some of these men turned out to have cancer: most likely, it was already there, and as urologist Patrick C. Walsh, M.D., says, although it may be possible to delay or slow growth, once cancer is present “you can’t unring the bell.” In studies published in the Journal of Pathology and Cancer Prevention Research, scientists Michael Haffner, M.D., Angelo De Marzo, M.D., Ph.D., Nelson, and colleagues have suggested — using new technologies that allowed them to look at the DNA of PIN and prostate cancer — that many areas of high-grade PIN are not cancer precursors at all. “Rather,” Nelson explains, “these PIN lesions actually reflect the growth of established cancer into prostate ducts. This may explain why some men with isolated high-grade PIN prove to have cancer on a subsequent biopsy,” and why, so far, no dietary agents have proven successful at preventing cancer in clinical trials.

“Going forward, we hope to be able to figure out which PIN lesions are actually cancer, and which are just precursors but not yet cancer,” says Nelson. “Of course, cancer growing in ducts should be treated like cancer, and with what we know now, cancer precursors require no immediate treatment. In the future, with a better sense of which men have PIN only, we may revisit clinical trials of agents that might prevent PIN from ever becoming cancer.”

Reassurance for Men on Active Surveillance

As many as 5 percent of men on active surveillance drop out of it every year – not necessarily because their prostate cancer has gotten worse, but because they hate the uncertainty.

Urologist H. Ballentine Carter, M.D., believes a new computer program will help. The program was designed with funding from the Patrick C. Walsh Prostate Cancer Research Fund and the Patient Centered Outcomes Research Institute. Two scientists from the Bloomberg School of Public Health, Yates Coley, Ph.D., a postdoctoral fellow, and Scott Zeger, Ph.D., a biostatistician, compiled 20 years’ worth of results from men in the Brady’s Active Surveillance Program — repeated PSA measures and prostate biopsy results — to make a predictive model.
“The model informs men about the likely future results of PSA tests and prostate biopsies,” says Carter, “and also predicts what type of cancer would be found if the prostate was removed and thoroughly examined. This patient support tool will help men make informed decisions, and when appropriate, reassure them that remaining in surveillance is safe.” An example of the model can be viewed at: https://rycoley.shinyapps.io/dynamic-prostate-surveillance.

Breaking DNA and Killing Cancer

Some men who are treated for localized prostate cancer with radiation therapy also receive androgen deprivation therapy (ADT), or hormonal therapy. “Multiple studies have shown the striking benefits of reducing testosterone before and during a course of radiation therapy for men with Gleason 7-10 cancers, or those who have cancer that can be felt outside the prostate (stage T3),” says Theodore DeWeese, M.D., Chairman of the Department of Radiation Oncology and Molecular Radiation Science. “This has resulted in better control of cancer in the prostate, a decreased risk of cancer spreading, and an improvement in survival. In the laboratory, Hopkins scientists have found that depriving human prostate cancer cells and tumors of testosterone and then briefly replacing high-dose testosterone causes a large number of breaks in the DNA. This is good: if not repaired, DNA breaks can lead to cell death. “Radiation also leads to large amounts of DNA breaks in cancer cells, resulting in cell death,” says DeWeese. In work with Vasan Yegnasubramanian, M.D., Ph.D., DeWeese has found that “when testosterone and other drugs that bind to the androgen receptor of prostate cancer cells are combined with radiation, even greater number of DNA breaks occur, resulting in much greater tumor control.” These results are so promising that with postdoctoral fellow Jonathan Coulter, DeWeese and Yegnasubramanian are seeking the optimal combination of radiation and androgen receptor-binding drugs, “so that we can begin to test this in clinical trials.”

Precision Brachytherapy, Using Real-Time X-Rays

The key to killing prostate cancer with brachytherapy, or seed implantation, is precisely placed seeds, says Danny Song, M.D. He should know; he’s one of the best in the world at this – and he is always working to make the procedure even better. As precisely as the seeds are placed, he notes, “due to multiple factors, it is not unusual for the final seed distribution to be different from what was intended.” To address this, Song and a team of collaborators from the Whiting School of Engineering and Acoustic MedSystems developed and tested a prototype system that uses ultrasound and x-ray imaging during the procedure, with excellent results. They have nearly completed a Phase II trial testing a more refined, advanced version of this system. In their study of 45 patients, “we start the implants using standard ultrasound-guided seed localization, but near the end of the procedure, we take a set of x-rays and run a custom set of computer algorithms” to see whether the seeds are where they’re supposed to be. “This provides a ‘real-time’ image of the seed positions, and many patients were found to have gaps in their prostate seed coverage which otherwise would have been missed.”

Based on the x-rays, Song added an average of four seeds per procedure. Afterward, when he confirmed the seed placement with MRI and CT imaging, “all 45 patients had excellent levels of prostate dose and gland coverage,” with minimal levels of radiation exposure to the rectum and urethra. When compared to an earlier group of more than 150 men treated with the traditional approach, “prostate gland coverage was significantly better in the x-ray imaging group, and there was an encouraging trend toward lower doses to the rectum as well.” In a few months, the team plans to combine this system with “newer imaging methods which can show where cancer is located within the gland. This will allow for precision, ‘focal’ brachytherapy.” To read more online about this and other clinical trials at Hopkins, please see: http://www.hopkinsmedicine.org/radiation_ oncology/research/about_clinical_trials.html.

Zarif Wins PCF Young Investigator Award

Jelani Zarif, Ph.D., M.S., a postdoctoral fellow in the laboratory of Kenneth Pienta, M.D., was one of this year’s recipients of the highly coveted Prostate Cancer Foundation (PCF) Young Investigator award. Applicants from 15 countries, age 35 and younger, competed for one of 24 awards. Together, the awards represented a $5 million investment in the future of prostate cancer research. “This is an honor that I am extremely grateful for,” says Zarif. “My research will focus on targeting immune cells within the prostate tumor microenvironment. We believe that these cells aide in prostate tumor growth, supply metastasis-supportive factors, and allow tumors to circumvent therapy.”

Zarif was also honored for his work within the Baltimore community with the Dr. Martin Luther King, Jr. Community Service Award. He serves as a mentor in a college-readiness program called the Beautillion Scholars program and in the Medical Education Resources Initiative for Teens (MERIT) program, which aims to transform under-represented high school students into health-care leaders.
Where’s the Cancer?  
Now We Can See It

Is there any prostate cancer outside the prostate?  What if there are just a few cells?  No one has ever been able to see the answer to this question before.  But now, thanks to Steven Rowe, M.D., Ph.D., and Martin Pomper, M.D., Ph.D., in the Russell H. Morgan Department of Radiology and Radiological Science and a multidisciplinary team that includes chemists, biologists, radiologists, urologists, and oncologists, the answer is visible.

In pioneering work, the team has managed to link radioactive molecules to prostate-specific membrane antigen (PSMA), a substance on the outside of prostate cells. These molecules show up on PET scans, and in studies, the team has been able to “increase dramatically the detection of sites of prostate cancer in men who have newly diagnosed disease and are being treated with surgery, in men who have previously had surgery but whose lab tests now indicate that they have suffered a relapse, and in men with known widespread disease,” says Pomper.

This remarkable work already has helped tailor treatments in Hopkins patients with prostate cancer, and will soon be more widely available in larger clinical trials at Hopkins and other hospitals. Because of its promise — not only to see cancer but to target new treatment — the primary imaging agent developed, known as DCFPyL, has been licensed to Progenics Pharmaceuticals for commercial distribution. The radiotherapeutic agents made by the Hopkins team have been licensed to Advanced Accelerator Applications for commercial manufacturing.

Where the Cancer Is

What you’re seeing is something no one has ever been able to see before: all the sites of metastatic prostate cancer. Some of them are too small to show up on conventional imaging, and the only way we can see it now is that Martin Pomper and colleagues figured out how to “tag” individual prostate cancer cells with a radioactive dye that sticks to PSMA — prostate membrane-specific antigen. The red arrows point to new outcrops of cancer in unexpected places well beyond the pelvis, including the lungs and liver.

Now, that’s a lot of cancer, but it doesn’t mean that this cancer can’t be treated. Some of these areas may respond to hormonal therapy, some may be big enough to target with radiation, and some may respond to chemotherapy — including specialized, experimental treatment that uses this same PSMA-targeting approach. Knowing where the targets are is a huge step toward determining how to reach them.
Read About the Research You have Helped Make Possible.

THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND

We’re beginning our second decade!
Since 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 would not be possible without the tremendous and amazing generosity of our patients and friends. Here’s some of the exciting work this year’s award winners are doing, which wouldn’t be possible without your help.

2016 AWARDEES

Alex Baras, M.D., Ph.D.
The Peter Jay Sharp Foundation Scholar, Departments of Pathology, Urology, and Oncology

W. Nathaniel Brennen, Ph.D.
The R. Christian B. Evensen Scholar, Department of Oncology

Misop Han, M.D.
The Carolyn and Bill Stutt Scholar, Department of Urology

Paula Hurley, Ph.D.
The Beth W. and A. Ross Myers Scholar, Departments of Urology and Oncology

William Isaacs, Ph.D
The Virginia and Warren Schwerin Scholar, Departments of Urology and Oncology

Michael H. Johnson, M.D.
The Phyllis and Brian L. Harvey Scholar, Department of Urology

Marikki Laiho, M.D., Ph.D.
The Dr. and Mrs. Peter S. Bing Scholar, Departments of Radiation Oncology and Molecular Radiation Sciences and Oncology

Shawn Lupold, Ph.D.
The Nancy and Jim O’Neal Scholar, Departments of Urology and Oncology

Karen Sfanos, M.S., Ph.D.
The Irene and Bernard L. Schwartz Scholar, Departments of Pathology, Oncology, and Urology

Dan Stoianovici, Ph.D.
The Thomas C. Quirt and Jack W. Shay Scholar, Departments of Urology, Mechanical Engineering, Neurosurgery, Oncology

Is This Cancer Safe for Active Surveillance?
The ideal candidate for active surveillance is “a man with low-risk disease whose likelihood of progression is low without treatment,” says Misop Han, M.D., the David Hall McConnell Professor in Urology. Still, in case the cancer is more aggressive than it seems, “we follow these men closely, and we recommend treatment if the disease progresses.” Despite its “demonstrated long-term overall safety and effectiveness,” there remains a “what-if” quality to active surveillance. “Active surveillance is not as widely used as it could be, because we have limited ability to accurately assess risk and detect cancer progression. There is a critical need to find accurate biomarkers that can discriminate indolent from potentially lethal prostate cancer.”

One of the most promising biomarkers is one that actually vanishes in aggressive prostate cancer: a tumor suppressor gene called PTEN. From studies led by Hopkins pathologists looking at biopsy tissue and removed prostate specimens after radical prostatectomy, we know that “PTEN is the most commonly inactivated tumor suppressor in prostate cancer,” Han notes. “This PTEN deletion is associated with aggressive clinicopathologic features and worse prognosis.” Another common genetic change in prostate cancer is rearrangement of a gene called ERG. Together, these two findings make a powerful case for aggressive cancer — the kind of cancer that should not be treated with active surveillance. With pathologist Tamara Lotan, M.D., and support from the Patrick C. Walsh Prostate Cancer Research Fund, Han proposes “to improve the risk stratification of patients in active surveillance by validating PTEN loss/ERG rearrangement as a biomarker to stratify risk, and make sure that men on active surveillance are at very low risk.”
Changing the Metabolism of Prostate Cancer

Some of the things that feed cancer are the same old things that feed us: fat, sugar, and protein.

Some of the things that feed cancer are the same old things that feed us: fat, sugar, and protein. Many cancers are glucose-dependent; sugar cranks up the metabolism and helps the cancer grow. An enzyme that makes RNA, called RNA polymerase, or Pol I, also helps feed cancer by driving up its protein production. Pol I is driven by the same factors that drive cancer, and by the loss of genes that are supposed to suppress cancer. In exciting work, cancer molecular biologist Marikki Laiho, M.D., Ph.D., and colleagues have shown in mice that targeting the Pol I enzyme can slow the rate of growth in prostate cancer.

So that’s sugar and protein. What about fat? With support from the Patrick C. Walsh Prostate Cancer Research Fund, Laiho, with Nathaniel Brennen, Ph.D., Brian Simons, D.V.M., Ph.D., and Samuel Denneade, M.D., are going after that, too. “Remarkably, prostate cholesterol content and synthesis equals that of the liver,” says Laiho. “In this project we will test a linkage between Pol I and the metabolism of lipids,” cholesterol and fat, “and implement combined therapies for synergistic targeting of prostate cancer cells.”

They will be looking for what Laiho calls the “crosstalk” between prostate cancer and the stroma, the tissue in between the cells. They hope that by blocking Pol I and blocking fat metabolism, as well, the dual-pronged effort will be more powerful than either approach by itself. “These studies outline a conceptually new approach that exploits the metabolic dependencies of prostate cancer, and may slow down cancer growth, or delay it altogether.”

Is Active Surveillance Right For You? What Do Your Genes Say?

In recent research (see Page 9), William Isaacs, Ph.D., and colleagues have shown that some genes nobody expected to be involved with prostate cancer — such as the hereditary breast cancer genes BRCA1 and 2 — may in fact, be lethal. These are faulty “mismatch repair” genes, and they can be inherited from your mother and father, and by your sons and daughters. These genes may be the reason why some men who otherwise appear to be perfect candidates for active surveillance go on to develop high-grade cancer.

These faulty genes may be the reason why some men who otherwise appear to be perfect candidates for active surveillance go on to develop high-grade cancer.

“Most men with prostate cancer have small, almost normal appearing cancers which are confined to the prostate,” says Isaacs. “Most of these cancers are destined to remain non-life threatening even without treatment,” and for these men, active surveillance is a safe alternative to surgery or radiation therapy. However, “some men suspected of having only low-risk disease will later be found to have high-grade cancers. These men may even lose their curability window because they delay treatment.”

Is there any way to identify these men? Isaacs believes these DNA repair genes — genes that are known, and that can be identified in a simple blood test — may be the key. “Recently, we found that inherited mutations in DNA repair genes can significantly increase a man’s risk of developing lethal prostate cancer.” With urologist H. Ballentine Carter, M.D., and support from the Patrick C. Walsh Prostate Cancer Research Fund, Isaacs will look at the DNA of men who appear to be excellent candidates for active surveillance, and see if they carry any of these faulty genes. “We believe this information can be developed into a powerful tool to help determine which men can safely undergo active surveillance, and which men need to have their cancer treated immediately.”

Changing the Genes in Prostate Cancer

Just as our currency is the dollar, the body’s currency is protein. Every cell we have does whatever it does using proteins. The DNA, our genetic code, contains the instructions for how to print up more currency, or make a protein. Step one of protein-making is transcription: the cell makes a copy, or a transcript, of the DNA. This copy is called RNA. Then, the RNA gets converted, or translated, into a chain of amino acids, and voilà — a protein is born. Thus, RNA translates genes into working proteins. Back to our dollar image: just as the government embeds special images into paper money so it can’t be counterfeited, the body adds something, too. “A key regulatory element, the polyA tail, is added to the end of every protein-coding RNA,” says scientist Shawn Lupold, Ph.D. “This tail consists of hundreds of Adenosine nucleotides and serves to increase RNA stability.” Think of a kite with a long string of flags hanging beneath it; these Adenosine flags are the building blocks of DNA. “PolyA tails can be introduced at different sites within each gene transcript, and the location of the polyA tail affects gene expression. Moreover, its location often differs between normal and cancerous cells.”
Could these genetic kite tails possibly affect the genes of prostate cancer? In work supported by the Patrick C. Walsh Prostate Cancer Research Fund, Lupold and co-investigator Srinivasan Yegnasubramanian, M.D., Ph.D. propose to “apply specialized RNA sequencing techniques to map the altered location of polyA tails in all genes expressed by prostate cancer,” Lupold says. “We hope we will uncover new cancer pathways and biomarkers. Secondly, we propose to modify the machinery that regulates where these polyA tails are located, to study its influence on prostate cancer and aggressiveness. These results may uncover new therapeutic targets for the management of aggressive prostate cancer.” Lupold has just been honored with a Distinguished Professorship. Please see Page 11.

Better than PSA: Proteomics?

As useful as PSA is, it doesn’t us all we need to know. “Unfortunately, PSA remains an imperfect marker for detecting cancer,” says urologist Michael Johnson, M.D., “and men with a ‘normal’ PSA may still harbor disease. Prostate biopsy only samples about 1 percent of the prostate. As a result, aggressive cancer can be missed.” Although PSA measurements taken over time can document the growth of prostate cancer, there is a more specific tickertape out there: proteomics.

Proteomics involves taking a very complex sample of proteins in the blood, or even in a few cells, and shining a powerful laser at it. The laser energy hits the proteins, smashes them and chucks them — think of extremely tiny Jackson Pollock paint splatters — at a detector. If Johnson can learn to decipher the proteomics of the normal prostate and prostate cancer at its various stages, by measuring all of the proteins in the blood, he may come up with entirely new snapshots for doctors to use.

In work supported by the Patrick C. Walsh Prostate Cancer Research Fund, Johnson will be comparing proteomic analyses on the blood of men who have undergone prostatectomy with the blood of men who have no prostate cancer; he will also be analyzing the proteins that show up in slow-growing prostate cancer and aggressive disease. “My goal is to discover new, highly accurate markers for early diagnosis of disease that could potentially be lethal,” he says.

Developing the Brady Genomics Portal

“The Brady Urological Institute, in conjunction with the Department of Pathology, has an unrivaled biorepository of prostate cancer,” says pathologist Alex Baras, M.D., Ph.D. But this amazing library of prostate cancer samples and data could be even better, he believes. Baras, with pathologist Tamara Lotan, M.D., and urologist Ashley Ross, M.D., Ph.D., plans “to leverage this unique resource to develop the Brady Genomics Portal,” taking the understanding of prostate cancer to a new level with new molecular and genetic characterizations of prostate cancer.

In work funded by the Patrick C. Walsh Prostate Cancer Research Fund, the investigators will examine the Natural History Cohort, “a data set that includes 356 men with intermediate- or high-risk prostate cancer,” Baras explains. The team will augment tissue samples from these tumors, which have had DNA and RNA extracted, with genomic studies characterizing gene mutations and copy number alterations. The team will integrate clinical and pathologic findings with the latest molecular information; their comprehensive results will be made available to Brady researchers and updated regularly. “We hope this will prove to be an invaluable and renewable resource for the Brady for years to come.”

THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND
Finding Those “One in a Billion” Cells

“Analyzing these cells presents the potential of a ‘liquid biopsy’ – studying cancer cells without having to extract them during a prostate biopsy.”

In prostate cancer, circulating tumor cells (CTCs) are cancer cells that have escaped the prostate and entered the bloodstream. The problem is, these elusive cells are few and far between – proverbial needles in the haystack, says Dan Stoianovici, Ph.D., Director of the Urology Robotics Program. And yet, finding them would be so helpful: “Analyzing these cells presents the potential of a 'liquid biopsy' – studying cancer cells without having to extract them during a prostate biopsy,” Stoianovici says. “It would also open a wide range of possibilities for personalized medicine. However, isolating these rare cells is very difficult due to their extremely small concentrations, as low as one in a billion of blood cells.”

If anyone can figure out how to do this, it’s Stoianovici, a brilliant scientist and Professor of Urology, Mechanical Engineering, Neurosurgery, and Oncology. With support from the Patrick C. Walsh Prostate Cancer Research Fund and with co-investigator Michael Gorin, M.D., he plans to design and build a novel device to isolate these cells from blood samples.

AR Mutations as a Predictor of Therapeutic Response

If hormonal therapy — blocking testosterone, also called “androgen deprivation therapy” — stops working in a man with metastatic prostate cancer, the next step is to go after the androgen receptor (AR). If testosterone is the key, then the androgen receptor is the lock it fits; sometimes, disabling the lock gives an extra benefit for these men. There’s a problem, however: “Some men become resistant to AR-targeting drugs,” says scientist Paula Hurley, Ph.D. It may be that these drugs don’t work because the androgen receptor defies the attempt to block it and keeps on functioning, “possibly through amplification or mutation of the AR gene.” In our last issue, Discovery reported on a test for a variant AR gene, called AR-V7, developed by Jun Luo and Emmanuel Antonarakis. For men who have this variant, the drugs enzalutamide and abiraterone do not work well.

If testosterone is the key, then the androgen receptor is the lock it fits; sometimes, disabling the lock gives an extra benefit.

These types of AR gene alterations are almost exclusively seen in patients treated with therapies blocking androgen-AR activity,” Hurley notes. “However, there is still a lot we don’t understand about these AR mutations. Confounding variables have hindered our ability to determine fully their predictive capability and biologic role. For example, the prevalence of each individual AR mutation remains low. But AR mutations often overlap, making it difficult to determine their individual contribution to resistance.”

We need a better understanding what these different mutations do, and how they interact, says Hurley. With support from the Patrick C. Walsh Prostate Cancer Research Fund, she will explore how these AR mutations affect a man’s response to anti-cancer drugs, with the hope of finding ways around these roadblocks — so the medicines can work better in the men who need them most.

Infection and Prostate Cancer

What bacteria are supposed to be in the urine?

There are lot of “microbiomes” around your body. These are little microclimates, with their own unique residents. For example, the bacteria that thrive in your gut are not the same bacteria that live on your hands. “Trillions of bacteria live in and on our bodies and they are ‘good;’ they help maintain our health, not hinder it,” says pathologist Karen Sfanos, Ph.D. “But, the healthy microbiome can be altered by things like diet or exposures to toxins and carcinogens.” In the prostate, she continues, “an altered microbiome can lead to infections and chronic inflammation, a condition that is linked to many types of disease, including cancer. Scientists have discovered recently that urine, long thought to be sterile, in fact is not. There are bacteria in there all the time, not just in the presence of an infection. “This recent discovery made us wonder whether infections that may cause chronic inflammation in the prostate could be caused by alterations to the normal urinary microbiome.” The first step in answering this question is to figure out what’s normal. What bacteria are supposed to be in the urine? “We have begun to profile the urinary microbiome in men with prostate cancer and in men without prostate cancer,” says Sfanos. In work supported by the Patrick C. Walsh Prostate Cancer Research Fund, with
co-investigator Angelo De Marzo, M.D., Ph.D., Sfanos will “conduct the first study that will visualize and localize bacterial species of interest. What we ultimately hope to achieve is to determine what a high-risk urinary microbiome is in terms of developing prostate cancer. If men can be tested for this high-risk urinary microbiome, it may be that they could be treated with specific antibiotics or anti-inflammatory drugs as a means to prevent prostate cancer development or progression.”

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**Restoring the Immune System’s Memory**

**In effect, prostate cancer throws dust in the eyes of T-cells, specialized white blood cells whose job is to kill cells it recognizes as the enemy. Then it gives them a case of amnesia.**

The immune system is extremely powerful — which is why one of prostate cancer’s first strategic attacks is to disable it. In effect, prostate cancer throws dust in the eyes of T-cells, specialized white blood cells whose job is to kill cells it recognizes as the enemy. Then it gives them a case of amnesia.

But the amnesia may be reversible, says W. Nathaniel Brennen, Ph.D., assistant professor of oncologist. It turns out that the immune system has its own version of a backup hard drive — “special T-cells that live in the bone marrow known as memory T-cells.” With support from the Patrick C. Walsh Prostate Cancer Research Fund, Brennen and oncologist Ivan Borrello, M.D., will go after these memory cells and use them to remind the T-cells involved in fighting prostate cancer that there are enemies close at hand that need to be destroyed.

“The good news is that the body stores memory of what the prostate cancer looks like on these special T-cells, which normally are maintained in a resting state,” says Brennen. In this investigation, he will “isolate these memory T-cells from the bone marrow, grow them outside the body, activate them using special techniques, and characterize their anti-tumor immune responses.” Though this has never been shown to work against prostate cancer, “extremely promising” results in other tumor types have been observed by Borrello. “The ultimate goal is to re-infuse these tumor-specific memory T-cells back into the patient to hunt and kill cancer cells spread throughout the body,” Brennen adds, “essentially, generating a personalized cancer immunotherapy platform.”
Who Should Have Chemotherapy Before Surgery?

Some people respond well to neoadjuvant chemotherapy, but others don’t.

Some people who have muscle-invasive bladder cancer do better if they receive cisplatin-based neoadjuvant chemotherapy before radical cystectomy, surgery to remove the bladder. The problem: the chemotherapy works very well in some people, and not so well in others. “Clinical trials have shown that patients who respond to chemotherapy before radical cystectomy are more likely to be cured,” says Trinity Bivalacqua, M.D., Ph.D., Director of Urologic Oncology. “But other people may do better with alternative treatments such as immunotherapy, so we need to be able to predict which patients will benefit from neoadjuvant chemotherapy.”

They may have found a way to point patients toward the treatment that will help them most: Recently, Bivalacqua and pathologist Alex Baras, M.D., Ph.D., analyzed biopsy tissue from Johns Hopkins patients with muscle-invasive bladder tissue. They found that a measurement called “tumor infiltrating (TIL) density” was strongly correlated with an important immune system factor, a “checkpoint inhibitor” called PD-L1.

“Intriguingly, our findings suggest that the immune system plays an important role in how the bladder responds to chemotherapy,” Bivalacqua says. “T-cells are great warriors in the immune system that attack cells the body perceives as the enemy. “We found a strong link between the ratio of T-cells (CD8) to Regulatory T cells TIL densities and the response to chemotherapy.”

This work, published in *Oncoimmunology*, represents the first report in bladder cancer showing that this ratio can predict who will respond well to neoadjuvant chemotherapy; combined with other genetic information about a patient’s particular tumor, this information “will help us guide patients to the treatments that will work best for them.”

Hope for the Future: An Engineered Bladder

“We envision developing a clinically functional, tissue-engineered bladder by the end of 2025,” says Trinity Bivalacqua, M.D., Ph.D., Director of Urologic Oncology. He and the Brady’s Regenerative Urology research team are working hard toward this goal, buoyed by recent breakthroughs in the practical mechanics of how to do it.

A collagen scaffold provides an elegant framework for the patient’s own cells to grow into a new bladder.

The key is a scaffold that allows the patient’s own cells to grow over it. Bivalacqua, is the first investigator to successfully complete a Phase 1 clinical trial in bladder cancer patients using this “autologous cell-seeded scaffold” to replace the urinary system after radical cystectomy. “Although the Phase 1 trial demonstrated regeneration of urinary tissue, the neo-urinary conduit was not durable,” so the team brainstormed and “outlined a road to success,” Bivalacqua says.

The interdisciplinary team includes Bivalacqua, a surgeon-scientist, Anirudha Singh, Ph.D., a biomaterials and tissue engineer, and Nikolai Sopko M.D., Ph.D., a stem cell biologist. Their strategy begins with designing more durable materials “that will function as urinary tissue for a long time. The use of regenerated urinary tissue is necessary.” Currently, replacement bladders are made using part of the patient’s own intestine; this is not ideal and complications are common.

Singh’s laboratory recently developed a novel process to make collagen scaffolds for “urological neo-organs.” Collagen, Bivalacqua explains, “is one of the most suitable biomaterials, and is a natural choice here.” But developing a good scaffold proved a tough challenge, “until Singh’s laboratory created a simple yet elegant collagen molding technology.”
which resembles synthetic polymer processing methods, to create neo-organs.” The versatile design has “unprecedented features and user-controlled mechanical and biological properties.” A patent is pending. “Specifically, this process developed hollow and tubular collagen systems ranging from ureter-like micro-sized tubings to tubes with designer lumen that resembles intestinal villi, to complex seaweed-like structures as multiple mini-bladders for regenerative urology applications.” This research is supported by the Greenberg Bladder Cancer Institute Foundation and the research findings will be published in Nature Biomedical Engineering. As Singh continues to refine the scaffolds, Bivalacqua and Sopko’s laboratories are developing animal models for testing them.

**Next-Generation Therapy for Early Bladder Cancer: Nanoparticles**

*It’s a very high-tech, miniaturized version of the “quicker picker-upper.”*

About 75 percent of people who have bladder cancer are diagnosed when it is in the early stage; this is non-muscle invasive bladder cancer (NMIBC). “The gold standard treatment for managing most NMIBC includes transurethral surgery to remove the tumor, followed by intravesical therapy (placed into the bladder) with bacillus Calmette-Guérin (BCG) vaccine,” says Trinity Bivalacqua, M.D., Ph.D., Director of Urologic Oncology. “However, half of the cancers treated with BCG vaccine recur.”

In clinical trials, chemotherapy drugs such as docetaxel and cisplatin are being tested on NMIBC that is unresponsive to BCG. However, when these drugs are placed in the bladder, they don’t easily penetrate into the tissue to reach cancerous cells, they’re rapidly cleared from the bladder, and they can enter the bloodstream, potentially causing systemic side effects. Maybe they need repackaging. Bivalacqua and urologist Max Kates, M.D., with colleagues Abhijit Date, Ph.D., and Laura Ensign-Hodges, Ph.D., have taken a novel approach, combining nanoparticles with “absorption-enhancing vehicles” that make sure most of the medicine gets absorbed by the bladder tissue, and less goes into the bloodstream. It’s a very high-tech, miniaturized version of the “quicker picker-upper.”

Based on successful lab tests of these novel nanoparticle combinations, Phase 1 clinical trials are in the works. These findings were published in European Urology.

**Is the Androgen Receptor also responsible for bladder cancer development and progression?**

Why is bladder cancer more than three times more common in men than in women? Maybe it has something to do with male hormones. Drugs that block male hormones, or androgens, are used to treat advanced prostate cancer; recently, Hopkins investigators led by Hiroshi Miyamoto, M.D., Ph.D., looked at the effects of several of these drugs on bladder cancer in the laboratory. **Drugs that block male hormones stop bladder cancer growth in mice, and may also help cisplatin work better.** They found that the enzalutamide, flutamide and bicalutamide could “inhibit the proliferation, migration, and invasion of androgen receptor-positive bladder cancer cells, and stop tumor growth in mice,” says Miyamoto. This work will be published in the journal, Urologic Oncology.
DISCOVERY IN KIDNEY CANCER

How Best To Treat Kidney Cancer: Evidence-Based Guidelines

An estimated 6,000 to 8,000 people undergo surgery each year for kidney tumors that are benign. Is this the best approach for them?

Every year, 60,000 Americans are diagnosed with kidney cancer. However, “not all kidney tumors are dangerous; in fact, many tumors are not even cancers,” says Mohamad Allaf, M.D., the recipient of the Mohamad E. Allaf Directorship in Minimally Invasive Urology and Director of Minimally Invasive and Robotic Surgery. An estimated 6,000 to 8,000 people undergo surgery each year for kidney tumors that are benign. Is this the best approach for them? This is one of “a number of uncertainties in the understanding of kidney cancer and its treatments,” says urologist Phillip Pierorazio, M.D., who also is Director of the Division of Testis Cancer. The established guidelines are in need of an update.

Allaf and Pierorazio, leading a team of Hopkins investigators, recently analyzed the literature and data on clinically localized kidney cancer to create new recommendations for the treatment of the disease. The project was funded by the Evidence-based Practice Center program of the Agency for Healthcare Research and Quality (AHRQ), a division of the U.S. Department of Health and Human Services. The team reviewed more than 20,000 articles and distilled the data into a document posted on the AHRQ’s Effective Healthcare Website (effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2185).

The team’s findings will help patients and physicians “predict which tumors are cancerous, how biopsy can be safely and effectively be used, and importantly, which treatment is right for a given patient,” notes Allaf. This document will help the American Urological Association prepare the newest guidelines for the treatment of kidney cancer.

Immunotherapy for Kidney Cancer: Who are the “Exceptional Responders?”

Checkpoint inhibitors are exciting new drugs that help the body’s immune system recognize cancer and attack it. “Tumors are able to turn off the immune system, but checkpoint inhibitors turn the immune system back on,” explains urologist Mark Ball, M.D. These drugs have achieved results considered miraculous in lung cancer, melanoma, and other cancers – in many cases, causing advanced tumors to melt away. They don’t work for everyone, and scientists are working hard to figure out why, so that these people can be helped, too.

“A small number of patients have long-term responses even after the drug is stopped.”

One of these drugs, called Nivolumab, has recently been approved as a treatment for metastatic kidney cancer. “Overall, between 20 to 30 percent of patients have a response to the drug,” says Kimmel Cancer Center scientist Chuck Drake, M.D., Ph.D. “More exciting, however, is that a small number of patients have long-term responses even after the drug is stopped.” Ball, who just completed his Brady residency, recently completed a study of these “exceptional responders,” along with Drake and surgeon-scientist Mohamad Allaf, M.D. They found that patients with exceptional response had more mutations in their tumors – making them easier for the immune system to recognize – plus higher numbers of CD8 T cells, particularly powerful immune cells that fight cancer. In these exceptional responders, too, certain genes were activated: “We found several genes that we did not know were involved in the mechanism of response to this drug,” Drake explains.

“This work may help us find out which patients will respond best to this drug,” says Allaf, and which patients will do better with different forms of treatment. These findings were presented at the Genitourinary Cancer Symposium in San Francisco and the American Urological Association’s annual meeting in San Diego.
Active Surveillance for Small Kidney Tumors

“Early data indicate that patients undergoing active surveillance have similarly excellent cancer survival rates when compared to patients undergoing immediate surgery.”

With kidney tumors, size matters: many tumors that are smaller than four centimeters are either benign or slow-growing cancers that may never need to be treated. Active surveillance is helping many people with these small tumors avoid unnecessary surgery. In 2009, urologist Phillip Pierorazio, M.D., started the DISSRM (Delayed Intervention and Surveillance for Small Renal Masses) Registry, a large, prospective trial that follows more than 600 people with small renal masses, and is its principle investigator. “Early data from the registry indicate that patients undergoing active surveillance have similarly excellent cancer survival rates when compared to patients undergoing immediate surgery,” says Pierorazio. These data were published in European Urology in 2015.

As part of the DISSRM Registry, patients regularly answer quality-of-life questionnaires; new data, recently published in the Journal of Urology, indicates that quality of life for these patients is not adversely affected by active surveillance. Patients choosing active surveillance tend to be older and to have other medical issues beside the small kidney tumor. Over time, quality of life improved, both for those who underwent surgery and those who remained on active surveillance, and was driven by improvements in perceptions of mental wellbeing. “It is very reassuring that our DISSRM program alleviates anxieties and makes people feel safe while under our care,” says Pierorazio.

Using Big Data to Beat Kidney Cancer

Urologic oncologist Michael Johnson, M.D., recent graduate of the Ralph T. and Dr. Hugh Judge Jewett Fellowship program and now on the Brady faculty, believes the key to improving kidney cancer care is to work smarter. “The cost of sequencing a human genome was sequenced in the 1970s,” he notes. “The cost of sequencing a human genome is approaching the cost of a CT scan. Yet, we don’t often use these data when treating kidney cancer. Why not?” One reason is that it’s hard for doctors to know what to do with so much data, and “that’s where Big Data computing comes in.”

“We are at a turning point in kidney cancer care, where we have more data than we know how to use.”

Johnson has teamed up with Kimmel Cancer Center scientist Charles Drake, M.D., Ph.D., to use a tumor’s specific genetic information to design personalized cancer therapy. With grant support from the National Institutes of Health’s Big Data to Knowledge Program, Johnson demonstrated that “neoantigens,” tumors with more genetic differences that can be detected by the immune system, are less likely to be aggressive. In a true translational research effort, he is performing DNA sequencing on selected kidney tumors that he removes during surgery. Then, using large-scale computing to predict neoantigens, he and Drake are testing ways to select and grow immune cell populations that recognize tumor-specific DNA changes. With support from the Greenberg Bladder Cancer Institute, he will also be taking the same approach with selected bladder cancer patients.

“We are at a turning point in kidney cancer care,” Johnson notes, “where we have more data than we know how to use. By combining surgery, bioinformatics, and immunology, we can transform our treatment by personalizing it for every patient.”

Testicular Cancer: High Cure Rates, Complex Treatment

The great news about testicular cancer is that “cure rates are exceptional, approaching 95 percent,” says Phillip Pierorazio, M.D., Director of the Division of Testis Cancer. However, “treatment can require timely, complex, multimodal strategies that most commonly include chemotherapy and surgery. One of the scariest things about testicular cancer is that it can grow very quickly, but that is also why it responds so well to most of our treatments.”

Although there are detailed treatment guidelines by the National Comprehensive Cancer Network and other groups, “outcomes for testicular cancer patients can vary dramatically among institutions,” Pierorazio adds. “The men who do best are at high-volume centers with experience treating the disease.”

But even high-volume centers don’t get it right all the time. Pierorazio recently teamed up with colleagues from the University of Chicago and University of Southern California to evaluate inappropriate, or non-guideline directed care, in their testicular cancer patients. “We found that 30 percent of their patients received treatment that differed from the recommendations.”

Most common were unneeded PET scans and “overtreatment in the form of too many chemotherapy cycles, or multiple drugs when one drug would have sufficed. Fortunately, few men were undertreated or received inappropriate treatments. It is difficult to expect every doctor to know the most appropriate and up-to-date treatments for a complex and rare disease. Therefore, testicular cancer should be treated at experienced centers of excellence.” These findings were published in the Journal of Urology.
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**THE BRADY: 100 YEARS**

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By Patrick C. Walsh and Janet Farrar Worthington

Featuring 380 Richly Illustrated Pages

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