

DISCOVERY

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The PSMA-Targeting Era:
A Game-Changer for
Men with Prostate
Cancer Worldwide

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Partin: Trained 45 residents, doubled The Brady's research space and expanded clinical outreach to the Green Spring Pavilion III.

Portrait: Alan Partin by Lisa Egeli, 2021, Oil on Canvas, Courtesy of The Alan Mason Chesney Medical Archives of The Johns Hopkins Medical Institutions

PARTIN STEPPING DOWN AS DIRECTOR

After 17 years, urologist Alan Partin, M.D., Ph.D., is stepping down as the Jakurski Family Director of The Brady Urological Institute, Urologist-in-Chief for Johns Hopkins Medicine, and Director of the Department of Urology. He will continue as an active member of The Brady, pursuing his work in clinical care, research, and education.

Under Partin's leadership, The Brady has doubled its research space, and undergone significant expansion with projects such as the world-renowned Greenberg Bladder Cancer Institute, and new clinical space at the Green Spring Station Pavilion III.

"Alan is a devoted teacher and mentor who is deeply committed to educating the next generation of clinicians and basic scientists," says Paul Rothman, M.D., Dean of the medical faculty and CEO of Johns Hopkins Medicine. "He has trained over 45 residents, including many women and people from underrepresented minority groups. He also has edited numerous urological textbooks and journals, and authored more than 600 scientific articles, publications, and presentations."

Partin's research has earned the British Association of Urological Surgeons' distinguished St. Paul's Medal and the American Urological Association's Gold Cystoscope Award and Distinguished Service Award. A *summa cum laude* graduate of the University of Mississippi, Partin has been at Johns Hopkins for nearly 40 years: he earned his M.D. at the School of Medicine, and his Ph.D. in pharmacology and molecular sciences. He did his residency at Hopkins and then joined The Brady as an associate professor in 1995.

"Alan's contributions to our institution and to the field of urology have been immeasurable," continues Rothman. "He is widely known and credited for his pioneering Partin Tables, which are used for predicting the prognosis for prostate cancer," and for his work in developing several innovative tests to identify and track prostate cancer, including the Prostate Health Index.

A national search is under way for Partin's successor, who will become The Brady's fifth Director, with large shoes to fill: in addition to Partin, previous Directors have been Hugh Hampton Young, William Wallace Scott, and Patrick C. Walsh. ■

COVER STORY: THE PSMA-Targeting Era

PSMA is tiny; you couldn't see it if you tried with the naked eye. It's just a protein, one of about 2 million in the human body. So why are doctors and patients so excited about it? Because of the company it keeps: PSMA (prostate-specific membrane antigen) lives in high concentrations on the surface of most prostate cancer cells, especially those with the highest lethal potential.

For the last nearly three decades, scientific pioneers including Martin G. Pomper, M.D., Ph.D., Director of Nuclear Medicine and Molecular Imaging and Professor of Radiology and Radiological Science, have been working on ways to use PSMA as a homing beacon for prostate cancer – particularly, for cancer that has left the prostate but is still too small to be seen by conventional imaging: CT, MRI, or bone scan.

In 2021, the FDA approved PSMA-PET imaging, in which a radioactive tracer that shows up in a PET scan is molecularly engineered to find one very specific target: PSMA. Because the tracer is injected systemically, it can shine a virtual spotlight on whatever it tags – even tiny bits of prostate cancer as small as a grain of rice – *anywhere in the body*. Several of these tracers have been studied. One, called ⁶⁸Ga-PSMA-11, received FDA approval for limited use at two hospitals in California: UCLA and UCSF. Another agent called PYLARIFY, (¹⁸F-DCFPyL, known as PyL), developed at Johns Hopkins by a team led by Pomper, is the latest to receive FDA approval and is much more widely available.

PyL has proven itself in two important clinical trials: CONDOR, published in *Clinical Cancer Research*, and OSPREY, which was published in the *Journal of Urology*. In the OSPREY trial, PyL PET/CT was tested in men diagnosed with high-risk, locally advanced prostate cancer who were set to undergo radical prostatectomy with pelvic lymphadenectomy, and in men with metastatic or recurrent cancer. In the

first group, the ability of PyL to detect metastases in the pelvic lymph nodes or beyond was determined, and in the second group, PyL was used to detect distant metastases. In both groups, it demonstrated excellent accuracy in detecting cancer with high specificity.

In the CONDOR study, men with a rising PSA after treatment for prostate cancer with surgery, radiation, or cryotherapy, who had no visible cancer on standard imaging, were scanned with PyL PET/CT, which accomplished what researchers hoped it would: “PyL successfully localized sites of disease in 85 percent of men with biochemical recurrence,” says Pomper, “even men with low PSA levels.” It detected disease in most men with biochemical recurrence presenting with negative or equivocal conventional imaging, and led to changes in management in the majority of patients.

“I’ve had patients for years asking me when we are going to be able to use this,” Pomper adds. “It’s proven very difficult, and taken a long time, but we are finally there.”

In 1996, Pomper was the first to figure out how to engineer a small-molecule, harmless radioactive tracer to PSMA, and his team went on to test the first PSMA-targeted PET agent in a clinical trial. Then, with a pilot grant from the Patrick C. Walsh Prostate Cancer Research Fund, he refined this into PyL, a more sensitive and specific agent that provides sharper images. “With standard imaging, we may suspect there is cancer outside the prostate area, but we often just can’t see it in its earliest stages. Standard imaging is not good enough for detecting and characterizing disease in men with biochemically recurrent prostate cancer, particularly in men with a low PSA (less than 2). But 95 percent of prostate cancer has PSMA.”

Who could benefit? For men with a rising PSA after treatment, men at high risk of cancer recurrence, or some men with metastatic prostate cancer, PSMA-PET can help determine what to do next. Two very exciting trials at Hopkins led by radiation

oncologist Phuoc Tran, M.D., Ph.D., have used PSMA-PET to guide stereotactic radiation therapy in men with oligo-metastasis – cancer that has not widely spread, but is in just a few isolated spots outside the prostate, with the idea that at this stage, cancer may still be curable.

A radioactive tracer, developed at Johns Hopkins with a pilot trial funded by the Patrick C. Walsh Prostate Cancer Research Fund, has become a game-changer for men with prostate cancer worldwide.

How is PyL different from ⁶⁸Ga-PSMA-11? Both are very good. PyL produces slightly sharper images due to the physics of its positron decay,” Pomper notes, “but the main difference is that ⁶⁸Ga-PSMA-11 requires special equipment to make, has a short half-life, and must be made in small batches on site in the hospital. PYLARIFY has a longer half-life, can be made in a factory and shipped ready to inject to any medical center able to perform PET imaging.” Although this is a radioactive compound, it is well-tolerated, he adds. “It has no pharmacological effect; it’s given in trace doses. It just binds to PSMA and goes away; it doesn’t do anything else to your body.”

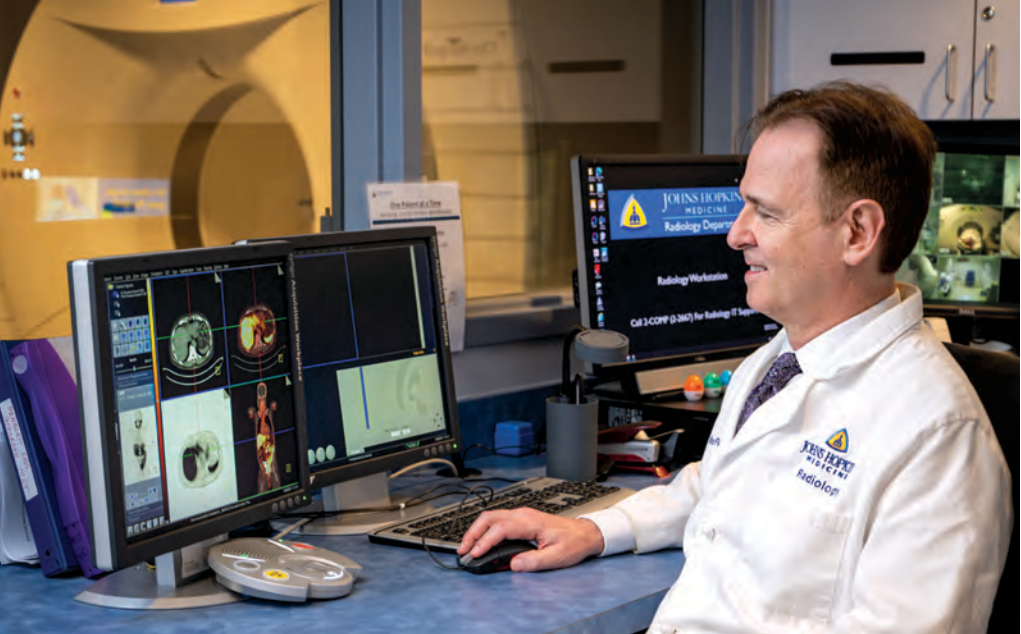
PSMA-Targeting Can Kill Cancer, Too!

But wait! This is not all that PSMA-targeting can do! Think of molecular LEGOS: Instead of attaching the tracer molecule that can “see” prostate cancer, a different isotope (chemical brick) can be attached: one that can kill cancer. “With the same chemical

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ON THE COVER

Martin Pomper's team developed a radioactive tracer, recently FDA-approved, that can show tiny bits of prostate cancer as small as a grain of rice.



Pomper: “We’re seeing exciting offshoots of our work in other forms of cancer, as well.”

continued »

scaffold serving as both a diagnostic and therapeutic agent, the field of theranostics has recently gained traction,” says Pomper. “Although I have been working on and off in this area for nearly 40 years, recent advances have really lit this form of treatment on fire.”

In Europe and Australia, and in international clinical trials, PSMA-targeting radionuclides such as ¹⁷⁷Lu-PSMA-617, are being used to kill metastatic prostate cancer. “In Australia, ¹⁷⁷Lu-PSMA-617 proved superior to cabazitaxel in terms of PSA response and lack of significant adverse effects when compared head-to-head in the TheraP trial,” says Pomper. “We are working with Novartis on a similar agent, called ¹⁷⁷Lu-PSMA-R2, which has even fewer side effects, including lack of uptake in salivary and lacrimal glands. We are hoping that agents using this molecular scaffold will be able to be outfitted with a variety of even more potent radionuclides than ¹⁷⁷Lu. It is anticipated that ¹⁷⁷Lu-PSMA-617 will be FDA approved at the end of this calendar year.”

What about the cancer cells that don’t make PSMA? Pomper is developing new molecules and therapies to target “PSMA-invisible” forms of prostate cancer. “We are working on agents that work through different mechanisms and can complement the PSMA-targeted agents,” he says. “I believe that combining theranostics with immunotherapy, PARP inhibitors and other emerging agents – in addition to further optimization of dosage, dose rate and type of isotope of

the PSMA-targeting agents – will be able to stave off progression of the disease for years, and that eventually, these patients will not die of their prostate cancer.”

There are even wider implications, too: “It took a long time, but now we’re seeing many exciting offshoots of our work in other forms of cancer, as well. Some pretty amazing things are happening.” ■

GOODBYE, CT AND BONE SCANS?

The National Comprehensive Cancer Network (NCCN) has recognizing the increased sensitivity and specificity of PSMA-PET compared to conventional imaging (CT, MRI, bone scans) for detecting micrometastatic disease, at both initial staging and biochemical recurrence.

In new guidelines announced in September 2021, the NCCN no longer recommends conventional imaging as a necessary prerequisite to PSMA-PET; in fact, the NCCN’s panel states, “PSMA-PET/CT or PSMA-PET/MRI can serve as *equally effective*, if not *more effective* front-line imaging tools for these patients.”

In one fell swoop, PSMA-PET is changing the standard of care.

A Domino Chain of Discovery

Four decades ago, Patrick Walsh started an ongoing series of discoveries that transformed the field of prostate cancer research and treatment.

It started with a single discovery:

More than 40 years ago, radical prostatectomy (an operation invented in 1904 at the Brady by Hugh Hampton Young) was a dreaded operation, notorious for excessive bleeding and the grim side effects of incontinence and impotence. Patrick Walsh, M.D., *University Distinguished Service Professor Emeritus*, wanted to make it safer, and he did, with the discovery and development of surgical techniques to stop the terrible bleeding. Improved visibility, in turn, led to new intraoperative improvements that dramatically reduced the risk of incontinence.

And then came Walsh’s great discovery, in 1980, with Dutch urologist Pieter Donker, of the cavernous nerves, which control penile erections. Until then, their location – just outside the prostate – was unknown, and surgeons routinely sliced through them as they removed the prostate. Over the next 14 months, Walsh developed a surgical technique to identify and preserve these microscopic nerves and on April 26, 1982, Robert Hastings became the first patient to undergo a purposeful nerve-sparing radical retropubic prostatectomy. Recently, Hastings died at age 88, cancer-free, having lived a normal life.

Over the next decade, radical prostatectomy became the most common form of treatment for localized prostate cancer in younger men, and with the timely development of PSA testing to identify men with curable disease, deaths from prostate cancer rapidly declined.

From a research standpoint, this dramatic increase in surgery resulted in an immediate benefit: **for the first time, there was an abundance of prostate tissue for study.**

“In the fields of breast and colon cancer, tissue was always available for pathologic, biochemical and molecular analysis,” Walsh explains. “However, because surgery for prostate cancer was rarely performed, only tiny amounts of tissue obtained from needle biopsies were available for many years.” By 1990, radical prostatectomy had become one of the most common inpatient surgical procedures performed at Johns Hopkins Hospital, and the tissue it provided helped to transform the field. Here are just a few examples:

Partin Tables. In 1990, when PSA testing became routine, little was known about how to interpret the findings. “We were fortunate to have Daniel Chan, director of clinical chemistry,” says Walsh. “He had the foresight to save serum samples from the prior five years, which enabled us to define how PSA could best be used for diagnosis and prediction of outcome. From these studies, we learned that PSA levels could not be used for prediction without understanding the aggressiveness of the tumor. With the expertise of Jonathan Epstein, M.D., the *Reinhard Professor of Urologic Pathology*, we learned that the most aggressive cancers did not make much PSA. This revolutionary observation led to the Partin Tables, which helped patients understand their likelihood of being cured by surgery.”



Epstein's studies of tissue provided by radical prostatectomies at Johns Hopkins yielded groundbreaking discoveries that helped shape patient care.

Criteria for very low-risk prostate cancer.

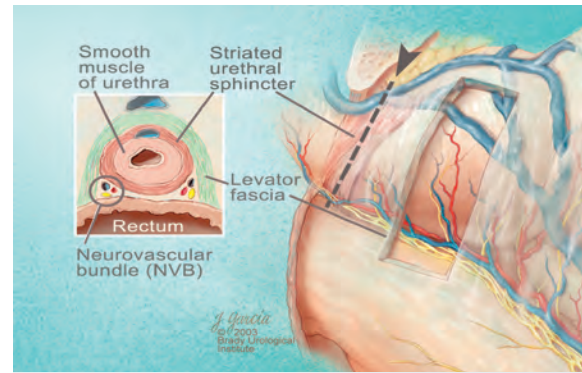
As more patients were being diagnosed with prostate cancer, scientists learned more about the spectrum of this disease. It became clear that many patients had tumors that were so small and slow-growing, they did not need immediate treatment. To identify which patients could be managed with active surveillance, Jonathan Epstein reviewed surgical specimens removed from patients who had small tumors. In 1993, he published the criteria that are still used for the prediction of very low-risk prostate cancer.

PSA elevation following surgery. It also became clear that after surgery, about 20 percent of men developed an elevated PSA, indicating that their cancer had recurred. “Based on the pathology of the surgical specimen, the time to PSA recurrence, and the speed at which PSA was rising (doubling time), we were able to develop recommendations for who did or did not require immediate treatment,” says Walsh.

Basic science discoveries. In the laboratory, legendary Brady scientist Donald Coffey, Ph.D., and colleagues used the tissue harvested at surgery for biochemical and molecular studies that shed light on how prostate cancer develops and what makes it aggressive. This insight into the biology of prostate cancer has played a major role in developing new approaches for treatment.

The world-class bio-database that made these studies possible began on day one 40 years ago, and today it contains specimens from 26,000 patients. This information (using patient codes and no names) is available to all Hopkins investigators who request it without charge or expectation for inclusion in authorship of manuscripts. “Someday,” says Walsh, “when surgery may no longer be necessary for the treatment of prostate cancer, historians may recognize that the tissue harvested from surgery in the past was instrumental in making the advances in treatment and prevention possible.”

This database has also made possible the pioneering genetic studies into Hereditary Prostate Cancer, which Walsh and William Isaacs first identified in the 1980s (see story on Page 10). ■



An illustration from Walsh's educational video, watched by urologists worldwide.

TEACHING THE SURGICAL TECHNIQUE TO THE WORLD

In 2003, Patrick Walsh produced a well-illustrated, one hour and forty-five-minute video that provided a detailed description of his surgical technique. Through the generosity of the Mr. and Mrs. Robert C. Baker Family Foundation, 50,000 complementary copies of the DVD were distributed to all urologists in the world who requested one. Today, urologists in China, Africa, India, and elsewhere attribute their ability to provide high-quality surgery to what this video taught them. The video remains widely available on the internet. www.youtube.com/watch?v=sasFpBlvXLg

Changing the Odds

Within a few miles of Johns Hopkins are thousands of men who have the highest risk of dying from aggressive prostate cancer in the world. They're at highest risk for many reasons, ranging from genetic – being of African descent – and environmental causes to disparities in health care, including a lack of early detection.

This can't go on, and changing it is going to take a whole community. But thanks to the help of a prostate cancer survivor, Fred Schaufeld, and his wife, Karen, change is starting to happen on many levels.

Schaufeld understands being at high risk for prostate cancer. It runs in his family, too: his father died of it, and so did his grandfather. Like many men with inherited risk (see story on Page 10), Schaufeld's cancer developed early. He was diagnosed in his 50s, and was successfully treated with radical prostatectomy at Johns Hopkins by surgeon Mohamad Allaf, M.D.

Now he and his wife are giving back generously, with a \$5 million commitment from the Fredrick D. and Karen G. Schaufeld Family Foundation to help the population of Black men in Baltimore and Washington, D.C. Their gift has established the **Schaufeld Program for Prostate Cancer in Black Men**, which will address the needs of this population at many levels, and will have three main components: *biomedical research*, with funded projects submitted by the best and brightest scientists at Johns Hopkins; *community partnership* for men and their families to raise awareness of risks, including lifestyle factors (such as smoking and diet), and to improve early detection and precision treatment; and *education* of healthcare providers and medical students.

The Schaufeld Program is co-directed by urologist Allaf, Director of Minimally Invasive and Robotic Surgery, and pathologist and molecular biologist Tamara Lotan, M.D., who has diagnosed more than 10,000 cases of prostate cancer and whose research focuses on molecular biomarkers of the disease. The research funded by the Program will not only help Black men, but will reveal new aspects of prostate cancer's mechanisms that could have implications for many men – and even, potentially, for treatment of other cancers, as well. Otis Brawley, M.D.,

Bloomberg Distinguished Professor of Oncology and an expert on cancer disparities, serves as Chief Advisor to the Program. Dina Lansey, M.S.N., Assistant Professor of Oncology, whose career focuses on understanding barriers to cancer care and developing interventions to address them, serves as Senior Advisor.

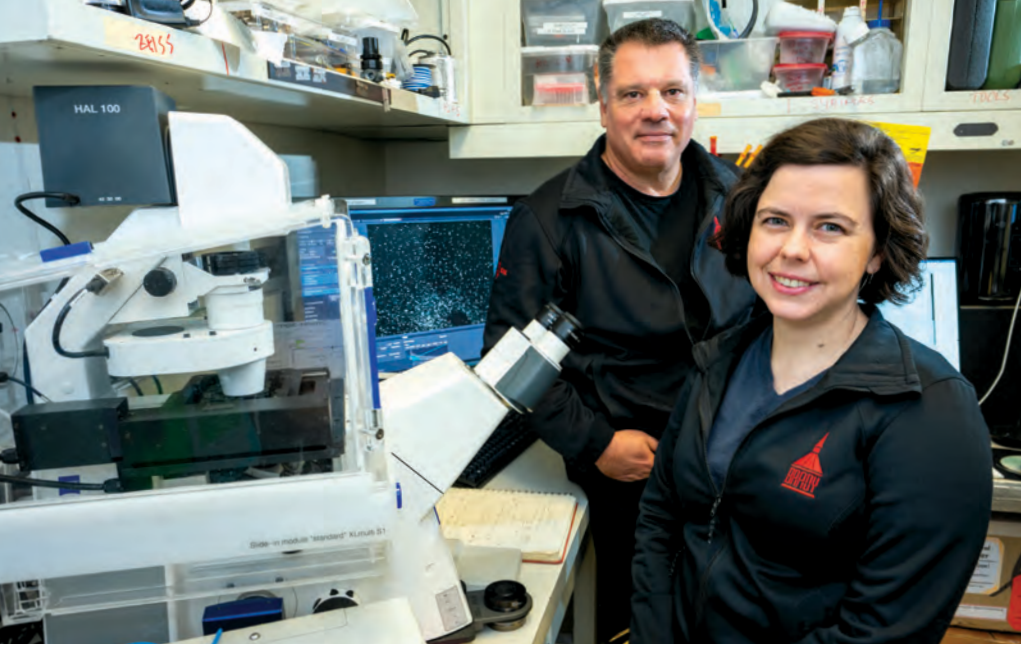
The Program does not propose to “reinvent the wheel,” says Allaf, but rather to leverage expertise and build on a strong health promotion model already in place, designed by Brawley and colleagues involving men in Baltimore and Prince George's County to provide evidence-based treatment and survivorship care among Black men who are already diagnosed with prostate cancer.

Nor will the Schaufeld Program be a case of Johns Hopkins swooping in and telling men what to do. Instead, the Program will work in tandem with city and church leaders, community members, local businesses and others, to reach Black men and their families. *Discovery* will continue to report on the Program's progress.

Please help us do more! If you would like to support this program, please contact Elissa Kohel in the Brady Development Office at ekohell@jhmi.edu / 410-955-8434. ■

Allaf, Lotan, Lansey and Brawley: *The Schaufeld Program combines biomedical research, community partnership, and education.*





Pienta and Amend: “Keystone” cells go into stealth mode and sleep right through prostate cancer treatment. Then they wake up and are even harder to kill.

Insights into Aggressive Cancer: Cellular Garbage Strikes and Sneaky Sleepers

Imagine New York City when the trash collectors have gone on strike: bags of garbage spilling onto the sidewalk and off the curb into the street. It’s pretty gross, and it immediately gets attention: everyone involved wants to see the problem solved quickly!

Something similar happens in cancer – and it might be a new target for treatment. Scientists Sarah Amend, Ph.D., Ken Pienta, M.D., and colleagues are very interested in a specialized type of immune cell, called an M2-like macrophage. Prostate cancer recruits these cells and makes them perform specific tasks, including the dirty job of “efferocytosis” – eating dying cells, or basically, taking out the trash. “While we generally think of cancer as only growing and proliferating, cell death is a natural part of tumor growth,” says Amend. “If these dying cells are not cleared by M2-like macrophages, they will trigger an anti-tumor immune response.” In other words, when the trash piles up, the body’s immune system sends soldiers to investigate.

This specific aspect of the tumor’s “ecosystem” is a promising target for therapy – either by itself or as a means of making cancer-killing drugs more effective. “By targeting MerTK, a critical receptor for efferocytosis by macrophages, we may be able to redirect the ecosystem engineering from pro-tumor to anti-tumor,” says Amend. Graduate student Kayla Myers is the trainee leading this work, which was published in *Cancer Control*.

In another major focus, the Amend and Pienta lab has been studying the phenomenon of polyan euploid cancer cells (PACCs) – which the group has dubbed “Keystone” cells, because they may hold the secret to treatment resistance in cancer. These cells have a very interesting response to cancer treatment: they sleep right through it. They go into stealth mode during the stress of treatment – like people hiding in a bunker during an air raid. Then, when the blitz is over, they emerge, “and repopulate tumors with progeny that are resistant to therapy,” says Pienta, the *Donald S. Coffey Professor of Urology*.

Pienta and Amend believe these Keystone cells are the major culprit in metastatic spread, cancer recurrence, therapeutic resistance, and – ultimately – lethality. “They go into a dormant state to protect DNA integrity and ensure cell survival,” says Amend. “Cancer cells in the PACC state avoid the stresses of the tumor microenvironment and the toxic effects of systemic therapy by going into cell cycle arrest.” That is, these cells stop growing and dividing; chemotherapy traditionally targets cells that are rapidly growing and dividing, as cancer does. In stealth mode, these Keystone cells slip right under chemotherapy’s radar.

After treatment, PACCs wake up, and “generate now-resistant progeny that make up the bulk of cancer cells within a tumor,” says Amend. “We have found PACCs to be viable, highly active cells capable of mediating metastasis and therapy resistance.” These research projects are driven by

graduate students Laurie Kostecka, Mikaela Mallin, Luke Loftus, Melvin Li, Anna Gonye, and Kevin Truskowski; and a postdoctoral fellow, Chi-Ju Kim, Ph.D. This work has been published in the *Proceedings of the National Academy of Sciences USA* and in *Seminars in Cancer Biology*. ■

STEPPING UP TO HELP

In the dark early months of the Covid-19 pandemic, there was a shortage of reliable Covid-19 tests. Hopkins scientists stepped into the breach: Drs. Elizabeth Jaffee and Mark Yarchoan led an effort to produce testing kits for use across Johns Hopkins Hospital. While research labs were shut down entirely for three months, eight Ph.D. students, postdoctoral fellows, and technicians, plus Pienta and Amend, volunteered their expert bench skills to help in the effort.

Working in shifts with other Hopkins scientists, they made more than 100,000 tests, keeping the Hospital supplied for several months. “Reagents and materials used to make these kits were donated by labs across the campus, including our own and others in the Brady,” says Amend. “We are proud of our lab team who donated their skills in a time of critical need, who stepped up to bring the same caliber of excellence they bring to their research to keep our community safe.”



Paller: Co-leader of PROMISE, a new registry of patients with inherited mutations in prostate cancer.

testing and access to a licensed genetic counselor to help them understand the results,” says Paller. For more information, go to prostatecancerPROMISE.org. ■

These findings “support that total cholesterol, apolipoproteins, and triglycerides may contribute to, or mark pathways that contribute to, the differential development of prostate cancer by disease aggressiveness, and by race.” ■

The PROMISE of Studying Inherited Genes

“Men who participate will get free, medical-grade, hereditary cancer risk testing and access to a licensed genetic counselor to help them understand the results.”

“Prostate cancer may be written in some men’s genes, but so are instructions for discovering new treatments and understanding family risk,” says oncologist Channing Paller, M.D. “That’s why learning more about the genes of men with prostate cancer is so important.”

With scientist Heather Cheng, Ph.D., of the University of Washington, Paller is leading PROMISE, a new registry of patients with germline mutations in prostate cancer. “We will screen 5,000 patients all over the country,” Paller says. “For 500 patients with specific inherited mutations, we will provide them with information about new standard treatments, as well as precision medicine clinical trials that match their genetic mutation. The other patients can opt in to learn more about clinical trials and treatment. This study will help bring a personalized approach to the treatment of prostate cancer.”

PROMISE is sponsored by the Prostate Cancer Consortium. The study is free, and patients can participate from home: men enroll online, receive a DNA test kit, and send back a saliva sample. The DNA test detects 30 genes commonly associated with hereditary cancers.

“Men who participate will get free, medical-grade, hereditary cancer risk

Cholesterol, Prostate Cancer, and Race

There’s a connection between cholesterol and the risk of aggressive prostate cancer. It’s not fully understood, and a new study by Johns Hopkins investigators has uncovered a further wrinkle: race.

Epidemiologist Elizabeth Platz, Sc.D., M.P.H., has been working for years to understand why men who are on statins, cholesterol-lowering drugs, seem to have a lower risk of dying of prostate cancer. Is it statins alone that lower risk? Could other cholesterol-lowering drugs, or even diet, accomplish the same effect? This is not clear.

It gets more complicated: cholesterol is not just one lump substance; it’s got components. There’s HDL (high-density lipoproteins, the “good” cholesterol) and LDL (low-density lipoproteins, the “bad” cholesterol). Further, there are apolipoproteins A and B (ApoB, an LDL component), and there are still other fats in the bloodstream, called triglycerides.

So: Does the risk come from total cholesterol itself, or does it vary with the sum of its parts? And are there racial differences? Recently, postdoctoral fellow Michael Marrone, Ph.D., M.P.H., (now on the faculty at Medical University of South Carolina), with Platz, Corinne Joshi, Ph.D., M.P.H., and colleagues conducted a study to find out more. They looked at data for 1,563 Black and 5,085 White men, participants in the Atherosclerosis Risk in Communities Study. The men were all cancer-free at their first visit, between 1987 and 1989. By 2015, 885 of these men had developed prostate cancer, and by 2018, 128 of them had died of it.

“We found that total cholesterol was associated with higher fatal prostate cancer risk in White men only,” says Platz. “ApoA was associated with higher fatal prostate cancer risk overall, but “ApoB was associated with higher fatal prostate cancer risk in Black men only.” Additionally, in Black men only, triglycerides were associated with higher total prostate cancer risk.”



In the study, the dogs detected Gleason 9 prostate cancer with 71 percent sensitivity and 73 percent specificity.

Why Can Dogs Detect Prostate Cancer?

Dogs can smell prostate cancer. In fact, out of a bunch of urine samples, they can even distinguish *aggressive* prostate cancer from low-risk or intermediate cancer.

Earlier this year, in an international project funded by the Prostate Cancer Foundation, Johns Hopkins scientists and collaborators in the U.S. and UK published a study in *PLOS One* showing that medical detection dogs could discriminate – with high accuracy – between urine samples from men who have prostate cancer and men who don’t.

What’s their secret? Nobody knows! But these investigators, including Alan Partin, M.D., Ph.D., *The Jakurski Family Director and Professor*, Karen Sfanos, Ph.D., M.S., and Bruce Trock, Ph.D., M.P.H., the *Frank Hinman, Jr., Professor of Urology*, are working to unravel the mystery of how the dogs do this – and just what it is that they are smelling on the molecular level – so their success can be replicated on a much larger scale.

“A more sensitive and specific detection strategy for lethal prostate cancer beyond PSA screening is urgently needed,” says Partin. “Although it’s not practical to use dogs as diagnostic sensors, machine olfaction for cancer detection is testable.”

Dogs with an excellent sense of smell can detect molecules in parts per trillion. In this study, using urine samples from biopsy-confirmed patients provided by Johns Hopkins, exceptional canines trained by Claire Guest of the UK-based group, Medical Detection Dogs, detected Gleason 9 prostate cancer with 71 percent sensitivity and 73 percent specificity.

Unfortunately, duplicating this electronically – using sensors that can detect “volatile organic compounds” (molecules of odor) – is not so easy. Guest explains why: “Prostate cancer is not going to turn out to be a single note. What dogs are really good at discovering is a tune. Think of Beethoven’s Fifth Symphony, those first few notes. We suspect the cancer signature is something like that. It’s a pattern; the dogs are really good at recognizing the pattern.”

What Exactly Are the Dogs Smelling?

It could be bacteria. Sfanos discovered several years ago that a basic medical assumption was just plain wrong: “We had always been told that urine was sterile,” she says. “It’s not.” Her research revealed that urine has its own microbiome – its own population of bacteria.

Could what the dogs are smelling be related to microbes in the urinary tract?” Sfanos was the ideal person to try to answer this question: she has access to an extensive biorepository at Hopkins, with thousands of urine samples that are linked to prostate pathology specimens. And in early research, she has found that men with aggressive prostate cancer – Gleason grade 9 – have different microbes in their urine than men with lower-grade cancer.

So: Could high-grade cancer be associated with its own particular population of bacteria, and could it be these bacteria that make the distinctive smell that the dogs can detect? This remains to be seen, but it’s quite possible. ■

For Advanced Prostate Cancer: Immunotherapy and... Testosterone?

Could the flat-out opposite of conventional wisdom prove to be effective against metastatic prostate cancer? Exciting

results of Hopkins-led studies are causing scientists to rethink androgen deprivation therapy (ADT) – the bedrock of treatment for advanced prostate cancer for more than half a century – and driving new approaches to tackle treatment resistance.

ADT slows down prostate cancer by shutting off testosterone. Eventually, however, cancer finds a way around ADT. Also, ADT has significant side effects, including fatigue, hot flashes, weight gain, and loss of sexual function.

Several years ago, medical oncologist Samuel Denmeade, M.D., Co-Director of the Prostate Cancer Program, and colleagues found a remarkable way to shake up cancer: alternating ADT with high-dose testosterone. Denmeade led a clinical trial of Bipolar Androgen Therapy (BAT) in men with metastatic prostate cancer, with promising results: “At the end of treatment, 70 percent of men remained responsive to ADT and only 30 percent had developed resistance.” During the testosterone period, quality of life and sexual function improved significantly and side effects were minimal.

“Overall, this study demonstrated that high-dose testosterone can be safely alternated with ADT as a means to improve quality of life and sexual function while potentially delaying the development of resistance,” he says. Denmeade then tested BAT in men who were resistant to ADT. “We found that many men responded to BAT. In addition, BAT was able to sensitize patients’ cancers to subsequent therapy to the antiandrogen, enzalutamide.”

Building on Denmeade’s work, Hopkins investigators Mark Markowski, M.D., Ph.D., and Emmanuel Antonarakis, M.D., (now Director of Genitourinary Oncology at the University of Minnesota) recently conducted a clinical trial of a whole new tactic: treating metastatic prostate cancer with a combination of high-dose testosterone and immunotherapy – and no ADT at all! “Although the treatment of metastatic prostate cancer generally involves *lowering* testosterone,” says Markowski, “we have studied the utility of testosterone *supplementation* as a primary form of therapy.”

In BAT, men experience high testosterone levels that decrease over a 28-day period, then bounce back up with the next

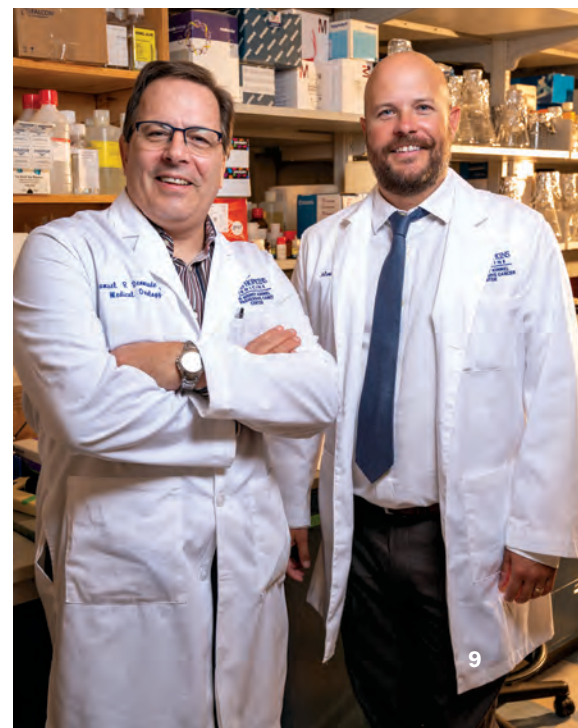
testosterone injection. “We have found that this monthly cycling can have a profound anti-cancer effect,” says Markowski.

“We found this monthly cycling can have a profound anti-cancer effect.”

In a related discovery, the Hopkins team also has observed significant clinical benefit in several patients who underwent immunotherapy after treatment with BAT. This led the team to conduct COMBAT, a small Phase 2 study involving 45 men with metastatic castration-resistant prostate cancer (mCRPC), who were treated with BAT in combination with nivolumab (an immunotherapy agent targeting PD-1). Their results were presented at the 2021 annual meeting of the American Society of Clinical Oncology. “We saw an impressive clinical response rate of 40 percent,” says Markowski. “We also observed a durable benefit, lasting over a year, in several patients who had received extensive prior therapies.” The combination of BAT with nivolumab was safe and well tolerated by the participants.

The next steps: Markowski, Denmeade and colleagues are working to identify a molecular profile of those patients with the deepest and longest-lasting responses. Markowski and Antonarakis are designing a randomized Phase 3 study to compare combined BAT plus nivolumab versus standard treatments for patients with mCRPC. ■

Denmeade and Markowski: Making metastatic prostate cancer more vulnerable to treatment by boosting testosterone.



The Patrick C. Walsh Hereditary Prostate Cancer Program

“To reduce deaths from prostate cancer, we must identify men at risk of lethal prostate cancer when cure is still possible. The best way to do that is through genetic testing.”

The Genetics of Higher Risk

In 1992, Brady investigators were the first to characterize and define hereditary prostate cancer (HPC). We now know that inherited genetic factors play a role in about half of all men with prostate cancer, and account for at least 10 to 15 percent of prostate cancer deaths.

Recently, groundbreaking work by William Isaacs, Ph.D. and colleagues showed that it's not just prostate cancer-specific genes that put a man at risk: DNA damage repair genes – known to raise the risk of other cancers – also raise a man's risk of dying of prostate cancer eightfold.

“To reduce deaths from prostate cancer, we must identify men at risk of lethal prostate cancer when cure is still possible,” says Patrick Walsh, M.D., who was Director of the Brady for three decades. “The best way to do that is through genetic testing.”

Since 2018, Isaacs and his team have sequenced more than 6,000 complete exomes (all the protein-coding segments in the genome) from men with prostate cancer. “Due to the disproportionately high risk of prostate cancer in Black men, we focused first on this population,

and completed next-generation sequencing of more than 1,600 Black men,” says Isaacs, the *William Thomas Gerrard, Mario Anthony Duhon and Jennifer and John Chalsty Professor of Urology*.

Early results are promising: “In this population, we have tentatively identified about 50 candidate genes with mutations – genes that were not previously thought to play a role in prostate cancer development.” In addition to these new genes, Isaacs' team, in collaboration with scientists at the University of Southern California, has identified “SNPs,” variant genetic sequences, in Black men; this work was published in *European Urology*.

Work by the team, including Isaacs' long-time collaborator, Jianfeng Xu, Ph.D., of NorthShore Research Institute, has resulted in 22 peer-reviewed publications in prostate cancer genetics over the last three years.

Predicting Multifocal Cancers:

More than 80 percent of primary prostate cancers are “multifocal;” they harbor two or more distinct sites of origin. Could this tendency be inherited? Isaacs, Xu, and Brady colleagues Christian Pavlovich, M.D. the *Bernard L. Schwartz*

Distinguished Professor in Urologic Oncology and Urology resident Yasin Bhanji, M.D., conducted a first-of-its-kind study to answer this question.

The investigators sequenced hundreds of SNPs known to be associated with prostate cancer risk to determine a genetic risk score (GRS), for more than 1,200 patients in active surveillance programs at Hopkins and NorthShore, and compared these findings with results of prostate biopsies.

They found that patients with a higher GRS are likely to have more positive tumor cores and bilateral (on both sides of the prostate) tumors. These results, published in *The Prostate*, suggest that inherited genetics can affect “whether a patient's prostate is likely to harbor multiple sites of cancer – and possibly,” says Isaacs, “even where these cancer lesions are most likely to be located!”

These findings could make prostate biopsies smarter and more effective. Several retrospective studies by the group have shown that adding GRS can improve detection rates in high-risk men, while reducing unnecessary biopsies in others. ■

A CHALLENGING OPPORTUNITY — “FOR THE FIRST TIME, WE HAVE THE POTENTIAL TO IDENTIFY EVERY GENE INVOLVED IN HPC, AND TO HELP THOUSANDS OF MEN AND THEIR FAMILIES UNDERSTAND THEIR FAMILY CANCER RISK, SEEK EARLY DETECTION AND TREATMENT, AND SAVE MANY LIVES.”

In 2018, urologist Patrick Walsh turned 80. The Brady wanted to honor this milestone, and asked Walsh for suggestions. His reply was immediate: to complete the work on hereditary prostate cancer (HPC) that Walsh and molecular biologist William Isaacs began 30 years ago. With the tremendous generosity of Walsh's current and former patients, The Brady established the Patrick C. Walsh Hereditary Prostate Cancer Program.

This is a mission for which The Brady is uniquely prepared: Over the last 30 years, with Walsh's leadership, we have built one of the world's largest collections of HPC samples, from more than 3,000 families and 8,000 individual patients, available for advanced DNA sequencing studies.

In exciting news, philanthropists and Brady Advisory Board members Beth and Ross Myers want to help complete this work, and have agreed to match all gifts to this program dollar for dollar up to a total of \$4 million, doubling the impact of each gift!

“For the first time,” says Isaacs, “we have the potential to identify every gene involved in HPC, and to help thousands of men and their families understand their family cancer risk, seek early detection and treatment, and save many lives.”

With your help, we can meet this goal! Please contact the Brady Development Office: bradydevelopment@jhmi.edu, 410-955-8434.

Read About the Research You Have Helped Make Possible.

THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND

How important is seed money? Priceless! Our cover story, on Martin Pomper's PSMA-targeting research, is an excellent example. That research got its start with one of the first-ever awards from the Patrick C. Walsh Prostate Cancer Research Fund. So did Samuel Denmeade's early work on BAT (see page 9). Since its inception in 2005, this remarkable Fund – made possible by the tremendous generosity of our patients and friends – 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. Their research has produced better ways to detect, treat and prevent the disease.

Applications are reviewed by a Scientific Advisory Board composed of noted Hopkins scientists and lay members. This year's awards are even more meaningful than usual, because they support dedicated research that has persisted in the midst of a global pandemic. These scientists should be proud, and so should you: *without you, their work wouldn't be possible!*

2021 AWARDEES

Sarah R. Amend, Ph.D.,
The Charlton C. and
F. Patrick Hughes Scholar
Department of Urology

W. Nathaniel Brennen, Ph.D.
The Mr. Keith L. Bremer Scholar,
Department of Urology

Arthur L. Burnett, M.D.,
The Beth W. and A. Ross Myers
Scholar, *Department of Urology*

Jonathan B. Coulter, Ph.D., M.H.S.,
The George and Mary Nell Berry
Scholar, *Departments of Urology,*
Oncology, and Radiation Oncology
and Molecular Radiation Sciences

Angelo M. De Marzo, M.D., Ph.D.,
The Frank E. Rath Spang & Company
Charitable Trust Scholar, *Departments*
of Urology, Pathology, and Oncology

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

Jun Luo, Ph.D.,
The Carolyn and Bill Stutt Scholar,
Departments of Urology and Oncology

Janielle P. Maynard, Ph.D.,
The Donald E. Graham Scholar,
Department of Pathology

Christian Pavlovich, M.D.,
The R. Christian B. Evensen Scholar,
Departments of Urology and Oncology

Outsmarting Cancer's Resistance to Therapy

Sarah Amend, Ph.D., believes the key to defeating metastatic cancer is to outsmart its “lynchpin of resistance,” polyaneploid cancer cells (PACCs), which put themselves into a dormant state to survive all known therapies. With the PCW Award, Amend is working to design innovative strategies to eliminate the PACC state. For more on PACCs, see story on page 7. ■

Testing a New Class of Drugs

Osmotic protoxins are new drugs custom-designed to seek out and kill only one target: prostate cancer cells. “These drugs are engineered to be inactive when traveling around the body,” says scientist Nathaniel Brennen, Ph.D., “significantly reducing side effects and toxicity to normal tissue. They activate when they reach prostate cancer cells, and kill them in a specific and highly efficient manner.”

How do they do that, exactly? By poking holes in the prostate cancer cell membrane. “This causes the cancer cells to pull in water, swelling until they burst open in a matter of hours – a process known as osmotic lysis.” Brennen knows these drugs are safe; scientist John Isaacs, Ph.D., and medical oncologist Samuel Denmeade, M.D., tested the first generation of this class of drugs, PRX302 (Topsalsyn), on

more than 500 patients in clinical trials for localized prostate cancer and BPH.

But “unfortunately, PRX302 can only be used as a local injection,” and metastatic cancer requires systemic therapy – an IV infusion that can travel throughout the body, looking for outlying cancer cells. “To overcome this limitation, we have engineered a second-generation version, known as APPX42, in which the protoxin is bound to human serum albumin,” explains Brennen. Like its predecessor, this protoxin is activated when it reaches prostate cancer cells. Because PRX302 has already proven safe in men with prostate cancer, Brennen expects APPX42 to begin clinical testing soon. ■

Facilitating Erection Recovery after Prostatectomy

Arthur Burnett, M.D., is a pioneer in the study of the nerves involved in erection. In animal models, he has shown that erythropoietin (EPO, a hormone that helps make red blood cells and raises hemoglobin levels, which increases blood oxygen), can help facilitate erection recovery after radical prostatectomy. “But no treatments have been established at the clinical level,” he says. “EPO's therapeutic potential as a neuroprotective agent has been shown to be promising in men,” but the FDA has been reluctant to approve it because of side effects associated with taking the drug

for a long period of time to treat chronic conditions. Burnett believes these side effects could be avoided by a limited use and proper dosage of this agent; however, EPO's role in the treatment of erectile dysfunction (ED) remains uncertain.

Another question: could EPO be made more effective in restoring potency and urinary control when combined with another agent – viable cryopreserved umbilical tissue (VCUT)? Burnett believes it could. “Our hypothesis is that this combination will increase the therapeutic benefit beyond the effect of either agent alone, based on their complementary, diverse neuro-protective mechanisms of action.”

Burnett will conduct a prospective randomized, double-blind, placebo-controlled, two-arm study designed to assess erectile function, urinary continence, and health-related quality of life. “We expect a gradual increase in erectile function and urinary continence postoperatively from baseline. This research could provide a meaningful advancement in quality of life for patients undergoing radical prostatectomy.” ■

BAF Complexes: Potential Targets?

“Much like modern computers, both normal and cancer cells have two competing, but essential tasks: to *store* massive amounts of data (such as DNA-encoding genes) and to access data,” says Jonathan Coulter, Ph.D., M.H.S. However, there are key differences, and here's a big one: prostate cancer cells arrange genetic data differently than non-cancerous prostate cells, and “these profound alterations are likely drivers of disease.”

Coulter's laboratory is uncovering critical components of “BAF complexes,” molecular machines that alter the 3-D architecture of genes in prostate cancer cells. “We are finding that prostate cancer cells use the androgen receptor to assemble these molecular machines,” says Coulter. Basically, the androgen receptor causes vast genomic reorganization in prostate cancer cells

– and this could be a vulnerability. “We hypothesize that these BAF complexes, which interpret various ‘grow or no-grow’ signals, may be key therapeutic targets. This could have implications on how we approach hormone therapies for prostate cancer patients or add additional therapeutic targets to our arsenal of prostate cancer treatments.”

Coulter's work suggests that being able to control the BAF complex could suppress the ability of prostate cancers to grow, adapt, and survive. He is beginning to describe the dynamic BAF complex assembly, and to characterize the specific roles these complexes may play in both growth of prostate cancers and their responses to therapies. ■

Slowing Down the Energizer Bunny

Innovative research from pathologist Angelo M. De Marzo, M.D., Ph.D., and colleagues may lead to a new way to target prostate cancer: by slowing down the cancer cell's battery pack– in effect, turning the Energizer Bunny into a slowpoke.

Cancer cells and normal cells have a battery, or power plant, called mitochondria. These mitochondria have their own DNA, and mitochondrial function is regulated by the copy number of mitochondrial DNA (mtDNA), which can be difficult to quantify. Recently, De Marzo and colleagues in his lab, Jiayu Chen and Qizhi Zheng, M.D., along with a longtime collaborator, Srinivasan Yegnasubramanian, M.D., Ph.D., developed a novel method to quantify mtDNA in specific cell types. They published an initial version of this method in the *American Journal of Pathology*, and presented later findings at the 2021 meeting of the American Association for Cancer Research.

In subsequent research, they found a direct correlation between the levels of mtDNA and dangerous cell changes: “We found elevated mtDNA in high-grade prostatic intraepithelial neoplasia (HGPIN) a known precursor

to prostate cancer,” says De Marzo. “Further, mtDNA was increased in prostate cancer, and even more so in metastatic prostate cancer. We implicated MYC, an oncogenic transcription factor, as a driver of these increases.”

In another collaboration with Yegnasubramanian and Ken Pienta, M.D., “using a completely different method entailing whole genome sequencing from laser-microdissected prostatectomy samples, we independently found increased mtDNA in prostate cancer.” Then, with Ralph Hruban, M.D., and Tatianna Larman, M.D., “we also observed elevated mtDNA levels *in situ* in pancreatic and colonic cancer precursors.”

The next steps include testing the hypothesis that increased mtDNA is a result of overexpression of MYC, “and whether this increase is required for the development of prostate cancer.” If this is the case, then inhibiting mtDNA replication with mitochondrial blockers might not only provide a novel approach to treating prostate cancer, but perhaps pancreatic and colon cancers, as well. ■

Expanding The Brady's HPC Database

William Isaacs, Ph.D., and colleagues have been working on understanding the molecular basis for hereditary prostate cancer (HPC) for nearly 30 years, and have built a priceless database of germline DNA samples from men with prostate cancer, with and without a family history of the disease. (You can read more about this research on page 10.)

“If we are to have a reasonable chance to find gene mutations which are important to developing prostate cancer, and – equally important – to find genetic markers which predict treatment response, we need to cast a wide net over a large number of cases,” he says.

The problem: the more cases, the more data – much more. “To date, we have generated over 40Tb, or

40,000,000,000,000 bytes of raw sequencing data,” says Isaacs, who will be overseeing a bioinformatics expansion “to put in place a well-organized, efficient and informative genomic data handling system. “Such a system will greatly increase our chances of finding genetic clues as to why some men develop and die from prostate cancer. It will also help us identify men at risk before cancer becomes incurable – and may even provide a basis for preventing this disease.” ■

What Drives Metastatic Cancer?

Scientist Janielle P. Maynard, Ph.D, and colleagues have identified a new mechanism that powers prostate cancer metastasis: a receptor called P2X4. “P2X4 belongs to the P2 purinergic receptor family, which is commonly upregulated in cancer and is associated with worse outcomes,” she says. “However, until now, the expression and function of specific P2 receptors in prostate cancer remained undefined.”

In Maynard’s previous research, she zeroed in on P2X4 receptors on prostate cancer cells in progression and metastasis. Then she expanded her study to look at the tumor microenvironment (TME); specifically, how the body’s immune cells interacted with this receptor. “Among the immune cells, we identified P2X4 positive (P2X4+) neutrophils and macrophages,” she says. She is looking to characterize P2X4 receptor expression in the TME, to determine what these receptors do “specifically on macrophages and neutrophils,” and in mice, to determine “whether loss of P2X4 receptor expression on macrophages and neutrophils affects how tumors initiate, progress, or metastasize.” P2X4-targeting drugs are already being investigated as treatments for other conditions. ■

MRI and Active Surveillance

What are the keys to success in active surveillance (AS) for prostate cancer?

There are two: one is choosing good candidates. “We only enroll men with a low risk of progression,” says urologist Christian Pavlovich, M.D. The other is careful monitoring: “Our patients are closely followed with serial exams, PSAs, prostate MRIs, and prostate biopsies.”

Over time, the AS Program at Johns Hopkins – one of the oldest and largest in the world – has developed a predictive model, “using relatively complex biostatistical methods and incorporating data from men who have been in the program over its many years. Our model uses age, PSA and biopsy information obtained over time to predict a man’s risk of progression to higher grade (more aggressive) cancer, so that treatment can be instituted before the cancer has spread outside the prostate.”

Pavlovich believes now is the time to improve this model, “by incorporating MRI information that patients obtain every few years, providing even more precise and accurate information to inform men when their cancer appears to be progressing, so they can be treated while they’re still in the window of curability.” ■

Finding Prostate Cancer Cells in Urine

Jun Luo, Ph.D., began looking for a more precise urine test for prostate cancer for a very good reason: “Among the roughly one million prostate biopsies performed annually in the United States alone, *the majority find no cancer*. In addition, prostate biopsies often result in the diagnosis of clinically insignificant cancers, contributing to prostate cancer overtreatment.”

What really need to be detected are the clinically significant cancers that, if not treated, will spread and may become lethal. There are commercial urine tests, but they use what Luo describes as a “grind-and-bind” approach, involving nucleic acid amplification, that has technical limitations. “A cell-based test, in which a cancer cell can be definitively identified under a microscope, would overcome such limitations,

and also achieve high specificity in cancer detection if cancer cells can be visualized.

Luo has developed technical approaches for a novel cell-based prostate cancer urine test that could be done right in the doctor’s office after a regular prostate check-up. “After a rectal exam, cells from the prostate are shed into the urine.” Using a process called RNA *in situ* hybridization (RISH), Luo’s test detects three prostate-specific RNA molecules: NKX3.1 (specific to cells of prostatic origin), PRAC-1 (specific to cells of prostatic origin but also increased in prostate cancer cells), and PCA3 (specific to prostate cancer cells).

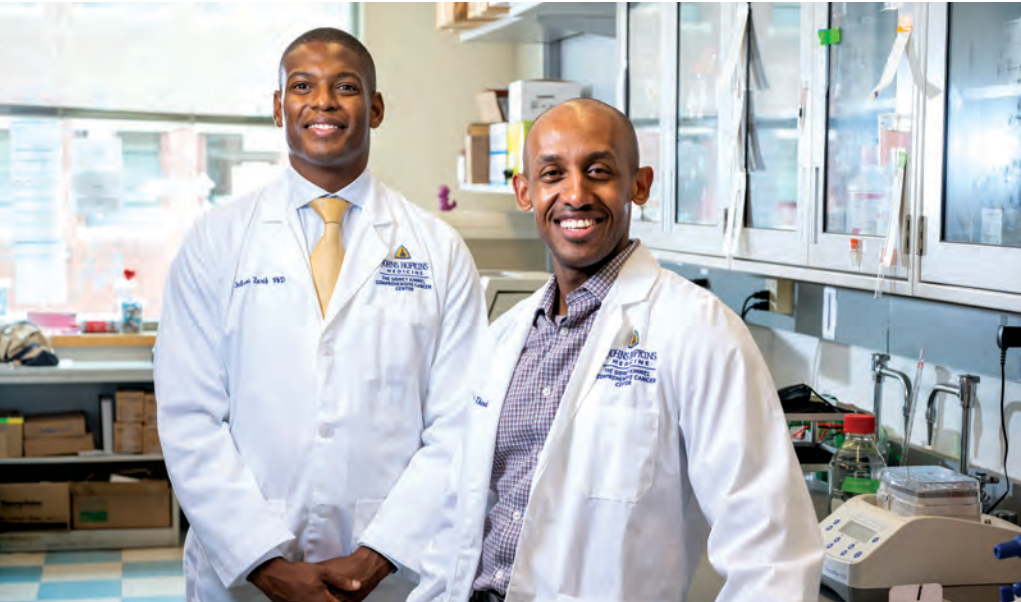
With urologist Christian Pavlovich, M.D., Luo validated this method and found it “enabled robust detection of malignant prostate cells in post-DRE urine sediments.” “The ability to directly visualize cancer cells in urine cytology specimens is a key advantage. We believe the test could be implemented in CLIA- or CAP-certified labs, given its capacity to predict significant cancer on biopsy with high specificity.”

In further research, he and Pavlovich will study the test in two groups of patients: men who need initial biopsy, and men already diagnosed with prostate cancer who are undergoing prostatectomy. ■



Luo and Pavlovich: This new method “enabled robust detection of malignant prostate cells” in urine.

MORE BRADY UROLOGY CANCER NEWS



Zarif and Theodros: In some cancers, myeloid cells “can be hijacked to suppress the immune system, to allow cancer to grow, progress and spread around the body.”

DISCOVERY IN KIDNEY CANCER

Team Discovers Unique Immune Cells in RCC

A team led by cancer immunologists Debebe Theodros, M.D., Ph.D., and Jelani Zarif, Ph.D., has found something new in renal cell carcinoma (RCC): the presence of unique, myeloid (resembling bone marrow) immune cells in tumors and nearby tissues in early, localized disease.

“When most people think of immune cells, they think of T cells or leukocytes, which recognize and destroy infectious bacteria, but can also attack cancer cells,” says Zarif. “Myeloid cells are a different type of immune cell, and in RCC and some other cancers, they can be hijacked by the cancer to suppress the immune system, to allow cancer to grow, progress and spread around the body.” This finding is promising, he adds: “The immune proteins related to these infiltrating myeloid cells may be targets for new therapies for patients with RCC.”

Zarif, Theodros, and other Hopkins scientists interested in RCC meet regularly as part of the Kidney Cancer Collaborative Program. This work, published in *Molecular Cellular Proteomics*, is one of the group’s first studies. ■

Renal Cell Carcinoma: Immunotherapy Before Nephrectomy

Checkpoint inhibitors may work best “when the kidney and kidney tumor are still in place, because there are more cancer cells and molecules for the immune system to recognize and treat.”

Checkpoint-inhibitor drugs unleash immune cells that have been inactivated by cancer, allowing the body to mount a powerful defense against cancer cells. In renal cell carcinoma (RCC), “these drugs have been shown to shrink tumors, prolong survival, and occasionally offer cures for patients in whom the cancer has spread,” says Mohamad Allaf, M.D., Director of Minimally Invasive and Robotic Surgery. New studies suggest that the timing of these drugs may make an important difference – that checkpoint inhibitors may work best “when the kidney and kidney tumor are still in place, because there are more cancer cells and molecules for the immune system to recognize and treat.”

In a recent investigation, published in *European Urology Oncology*, Allaf and colleagues administered nivolumab (a potent checkpoint inhibitor) before surgery in 17 patients with large or locally advanced RCC. The study was designed to prove the safety of this approach, and it did; patients had very few side effects and no surgical complications were attributed to the drug. But that’s not all the study showed: “Our early laboratory analyses indicate that the drug leads to promising immune infiltration of the tumors, and oncologic analyses demonstrate very few recurrences at two years.” This work was published in *European Urology Oncology*.

Building on this work, a large-scale, randomized clinical trial called PROSPER has treated about 700 patients with nivolumab before and just after nephrectomy; Allaf is the principal investigator of this study, as well. “We hope the results of PROSPER, coupled with our earlier results, will dramatically change the management of patients with RCC.” ■

RCC: Local Recurrence Can Be Cured with Surgery

“More than half of these patients were cured with a second surgery, and were able to avoid systemic chemotherapy.”

A small subset of patients with renal cell carcinoma (RCC) have a local recurrence – a return of cancer near the kidney, with no evidence of distant metastasis. “This is rare,” says urologist Nirmish Singla, M.D., M.Sc., who recently was part of a Brady team that looked at how these patients have fared at Johns Hopkins. “Of more than 3,000 patients with RCC treated at the Brady since 2004, we found that only 30 developed an isolated recurrence around or near the kidney. Our findings were encouraging: More than half of these patients were cured with a second surgery, and were able to avoid systemic chemotherapy.”

This work was published in *Urology*. The paper's first author, Shagnik Ray, M.D., a Johns Hopkins medical student, now is a Urology resident at Ohio State University. "This is an important study for patients with this rare recurrence," says Singla. "It provides data supporting an aggressive surgical approach for patients with localized disease, and offers hope for a cure." ■



Matoso: "We were able to identify groups of extremely aggressive cancers and those with a better prognosis."

"Unclassifiable" Kidney Cancer: New Insights

Most of the 60,000 Americans diagnosed yearly with renal cell carcinoma (RCC) have a type identified by pathologists as "clear-cell renal cell carcinoma," based on its characteristic appearance under the microscope. There are less common types of RCC, such as papillary and chromophobe – and then there are a number of kidney tumors each year that don't fit any of these categories, and thus are known as "unclassified RCC."

"A better understanding of unclassified RCC is needed to improve treatment for patients with these rare types of tumors," says pathologist Andres Matoso, M.D., who led a recent study to shed light on

these tumors. "We evaluated 79 patients with unclassified RCC and were able to accurately categorize those tumors, based on newly available pathological analyses," Matoso says. Although the team was not able to classify all the tumors, "we were able to identify groups of extremely aggressive cancers and those with a better prognosis. We hope these results will provide a pathway moving forward to clarify treatment." This work was published in the *American Journal of Surgical Pathology*. ■

DISCOVERY IN TESTICULAR CANCER

Ultrasound and Testicular Tumors

Not all testicular lumps – particularly, those smaller than 2 cm, as seen on ultrasound – are cancer; some are not. "Most men with a testicular mass greater than 2cm have cancer, but for many men with a mass less than 2cm, it is a benign growth on the testicle," says urologist Nirmish Singla, M.D. Thus, "testis-sparing surgeries are now in the arsenal for many expert centers that treat testicular cancer." In testis-sparing surgery, the mass is removed and analyzed in real-time for cancer. "Testicles with benign tumors can often be spared, while testicles with cancerous tumors are usually removed."

"Testis-sparing surgeries are now in the arsenal for many expert centers that treat testicular cancer."

In a study published in the *World Journal of Urology*, Hopkins researchers led by former resident Zeyad Schwen, M.D., now on the faculty at Cleveland Clinic, discovered that ultrasound often underestimates the size of sub-2cm testicle masses, and that determining the mass's volume may better characterize the risk of a benign or malignant testicular tumor. "These data help us counsel men about their risk of cancer and our ability to save the testicle," notes Singla. ■

New Guidance for Treating Early Testicular Cancer

Nearly all men with early-stage testicular cancer are cured.

What's the best treatment?

"The choices are not simple."

Most men (94 to 100 percent) with early-stage testicular cancer, confined to the testicle or lymph nodes that drain the testicles, are cured. "For these men, the difficulty is to determine the best treatment strategy," says urologist Phillip Pierorazio, M.D., "and the choices are not simple: active surveillance, chemotherapy, radiation therapy, or retroperitoneal lymph node dissection (RPLND). All are associated with significant risks, despite a uniform cure rate."

Surveillance has the highest risk of cancer recurrence (15 to 20 percent) but the lowest risk of unnecessary treatment. Chemotherapy and radiation therapy have low recurrence rates (less than 5 percent) but are associated with short-term toxicity, including nausea, vomiting, and fatigue, and long-term toxicity, including the risk of hearing loss, nerve issues, second cancers later in life, and early heart disease. RPLND is a major operation with significant short-term surgical risks but minimal long-term risks, and an intermediate risk of recurrence (5 to 10 percent).

"Patients can interpret these data and decide on the management strategy that best fits their values, their personality, and their lifestyle," says Pierorazio. "There is no wrong answer and no right answer." These findings, published in the *Journal of Urology*, serve as the foundation for the American Urological Association Guidelines for the Management of Early-Stage Testicular Cancer. The AUA funded this research project. ■

Men and Women Respond Differently to Immune Checkpoint Blockade

Immune checkpoints are like tiny brakes that immobilize immune cells that otherwise could be fighting cancer. In recent years, an entirely new class of drugs called “checkpoint inhibitors,” has emerged – but these drugs don’t work identically in everyone. That’s because the particular immune soldiers involved in cancer – the body has quite a few – can vary from person to person. And now, investigators from the Greenberg Bladder Cancer Institute (GBCI) have discovered that the immune response also varies between men and women.

Recently, a team of investigators led by medical oncologist Burles “Rusty” Johnson, M.D., Ph.D., looked to see whether the presence of intratumoral B cells (immune cells that have been linked to a better response in melanoma) was associated with clinical benefit from the immune checkpoint inhibitor, atezolizumab (Tecentriq) in patients with advanced urothelial cancers.

“We found that patients who had the longest survival were those whose tumors expressed high levels of the B cell gene expression signature and high levels of a CD8+ T cell gene expression signature (B8T high/high),” says Johnson. But the team was surprised to find something else, too: “Strikingly, breakdown of the results by gender revealed that this enhanced benefit was restricted to men. Women with B8T high/high tumors did not have a survival advantage.”

There was one more twist: “Interestingly, the *opposite* pattern was observed in patients with muscle-invasive cancer who were not treated with checkpoint inhibitors,” Johnson adds: “Women with B8T high/high tumors had the best outcomes.” Although the results require validation in additional independent cohorts, they suggest that the combined B8T signature could be used to identify the men with bladder cancer who will derive the most benefit from modern immunotherapy. These results were published in *European Urology Oncology*. ■

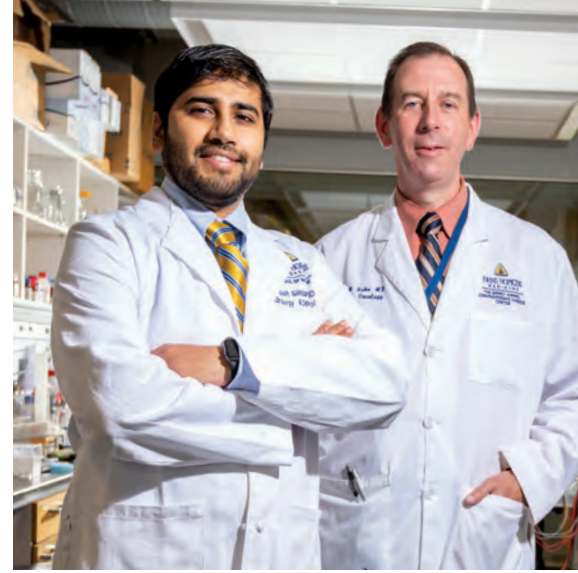
Treatment Goals for NMIBC: What Do Patients Think?

In recent years, new clinical trial guidelines from the Food and Drug Administration (FDA) have stimulated the development of new drugs for non-muscle-invasive bladder cancer (NMIBC). However, input from patients has been lacking – particularly, patients’ perspectives on the toxicity of these drugs in relation to clinical benefits, says medical oncologist Noah Hahn, M.D., Deputy Director of the Greenberg Bladder Cancer Institute.

Hahn recently led a multidisciplinary working group that conducted a nationwide survey on key issues related to treatment for NMIBC. The group investigated differences in responses among 845 patients, caregivers, and health-care providers; this work was supported by the Bladder Cancer Advocacy Network. Hahn presented the investigators’ initial results at the 2021 Genitourinary Cancers Symposium, held virtually in February.

“We observed no significant differences among patients, caregivers, urologists, or oncologists with regard to acceptable rates of any reversible or irreversible toxicities,” Hahn says. “However, oncologists accepted higher rates of urologic toxicities, including burning with urination, urine leakage, and urinary frequency, as well as immune-related side effects such as rash, diabetes, and need for steroids.” Complete response to treatment was consistently ranked lowest in clinical relevance among all respondents, but “freedom from cystectomy (surgical bladder removal) and freedom from progression to muscle-invasive disease consistently ranked highest.”

These survey results “suggest an increased emphasis on bladder preservation and durability of response in future clinical trial design guidelines and when evaluating the merits of new NMIBC therapies.” ■



Singla and Hahn: Leading research efforts to bring more and better treatments to patients with genitourinary cancers.

Neoadjuvant Chemotherapy and Muscle-Invasive Bladder Cancer

Having one or more mutated DNA damage repair (DDR) genes – “spell-checkers” that normally stop faulty genes from replicating – has been linked to a better response to neoadjuvant (presurgical) chemotherapy in muscle-invasive bladder cancer (MIBC).

But Johns Hopkins investigators have found that it’s not that simple. Under the direction of Trinity Bivalacqua, M.D., Ph.D., Brady resident Russell Becker, M.D., Ph.D., performed a retrospective analysis of the connection between aggressive clinical (based on biopsy) restaging and subsequent pathological (definitive, based on surgically removed tissue) staging in patients at Johns Hopkins who were treated with neoadjuvant chemotherapy. The team also performed next-generation sequencing on pretreatment tumor tissues to examine how well the presence of mutated DDR genes predicted pathological response.

Their findings were sobering: “We found that clinical restaging missed residual MIBC in almost one third of patients,” says Becker, and that response to neoadjuvant chemotherapy was not determined by the presence of DDR mutations. “The results represent a cautionary note for our ongoing clinical trials, and indicate that more accurate methods of detecting residual disease must be developed before neoadjuvant therapies can be used for organ preservation.” These results were published in *European Urology*. ■

Spotlight on UTUC

An estimated 9,000 Americans each year are diagnosed with upper tract urothelial cancer (UTUC), which affects the renal pelvis or ureter and is difficult to treat. Greenberg Bladder Cancer Institute clinicians and scientists are pioneering innovative treatments to manage this rare, complex disease.

Topical Therapy for Low-Grade UTUC: Hydrogel Helps Save the Kidney

One of the challenges of treating low-grade UTUC is its location: the ureter, the tube that conveys urine from each kidney to the bladder, is very narrow; about 4 mm or less in diameter.

“The small size of the ureter has prevented adequate treatment with current technologies – until now,” says urologist Phillip Pierorazio, M.D. A novel hydrogel may be the game-changer doctors and patients have been waiting for. “This hydrogel is liquid when cooled, but it solidifies as it warms to body temperature. It can be infused with chemotherapy and delivered into the kidney to treat UTUC topically.”

The chemotherapy used in this case is Mitomycin C, a proven performer in bladder cancer, Pierorazio adds. “It’s very effective at killing urothelial cancers, and works great in the bladder.” The hydrogel is essential in getting – and keeping – the drug in place. “Before this drug became available, we had no means to get chemotherapy to stay in the kidney. Normal urine flow would wash it out before the drug could kill the cancer.”

The hydrogel, called Jelmyto, takes six hours to dissolve and release chemotherapy after it solidifies in the kidney. Pierorazio and colleagues at Hopkins were investigators in the first clinical trial using Mitomycin C for patients with low-grade UTUC. The trial’s results, published in *Lancet Oncology*, found no evidence of cancer one year after treatment in 60 percent of patients.

While up to 40 percent of patients experienced an inflammatory narrowing of the ureter, for nearly all of them, these symptoms were transient, and almost all patients were able to preserve their kidney. “This is a major paradigm shift for patients with low-grade UTUC,” says Nirmish Singla, M.D., M.Sc., Director of Translational Research in Genitourinary

Oncology and Co-Director of the UTUC multidisciplinary clinic (see next story). “Previously, all we had to offer were ineffective technologies or radical surgery. Now we have a topical therapy, and we expect more therapies to emerge in the coming years.” Hopkins is also a site for the ENLIGHTENED study, which will investigate a laser-based photodynamic therapy to ablate UTUC in the renal pelvis. ■

Multidisciplinary Clinic for Patients with UTUC

For more than 130 years, Johns Hopkins has provided expertise in treating difficult and rare diseases that doctors at some hospitals might never even come across: diseases like UTUC.

“UTUC is a rare and challenging cancer to manage, accounting for only 5 to 10 percent of all urothelial tumors,” says Nirmish Singla, M.D., M.Sc., “Treatment approaches have traditionally been extrapolated from bladder cancer, but mounting evidence suggests that UTUC and bladder cancers are actually disparate entities.”

For example: tobacco exposure is the most common risk factor for developing either UTUC or bladder cancer, but UTUC also has other risk factors, including Lynch syndrome (an inherited condition that raises the risk of many types of cancer) and exposure to aristolochic acid (found in some Chinese herbal medicines and also sold as weight-loss aids).

Furthermore, Singla continues, “UTUC is inherently subject to diagnostic and staging challenges, including both the technical challenges of biopsying tumors in the upper urinary tract and the limitations of conventional cross-sectional imaging. The gold standard approach to surgically treating UTUC, radical nephroureterectomy (removal of the renal pelvis, kidney, ureter, and bladder cuff), is not without consequences, either, as it places patients at risk of chronic kidney disease.” Given the rarity of UTUC and the complexities of its management, very few centers nationwide have expertise in caring for patients with UTUC.

Recent clinical trials have shown a benefit to integrating systemic therapy with surgery in treating high-risk UTUC. “Thus, access to a multidisciplinary care team that includes an experienced urologic surgeon and genitourinary medical oncologist is paramount to

optimizing outcomes in patients with UTUC,” says medical oncologist Jean Hoffman-Censits, M.D., Co-Director of the Women’s Bladder Cancer Program at the Sidney Kimmel Cancer Center.

Recognizing this critical need, as of June 2021, Johns Hopkins offers such a team, co-directed by Hoffman-Censits and Singla. The Clinic, held twice per month, offers streamlined, “one-stop,” personalized care from multiple specialists for patients with this rare and complex disease. Patients will also be able to take part in clinical trials and research studies. The clinic will be expanding to include specialists from other disciplines, including nephrology and genetics. ■

Same Patient, Different Types of Bladder Cancer

Some patients with cancer in one part of the bladder develop cancer in another part – and these cancers may be made up of different cells, have different biomarkers, and may require different treatment.

“Upper tract and lower tract bladder cancers often arise in the same patients, but the biological relationships between them are not clear,” says David McConkey, Ph.D., the *Erwin and Stephanie Greenberg Professor of Urology* and Director of the Greenberg Bladder Cancer Institute.

Recently, McConkey and colleagues performed RNA sequencing on upper tract urothelial carcinoma (UTUC) and bladder cancers and examined the tumors’ biological properties. “We found that the tumors could be grouped into two subsets: one that was enriched with biomarkers characteristic of bladder cancer luminal subtypes, and the other that was enriched with basal-like biomarkers. Interestingly, most of the bladder-then-upper tract cancers were concentrated in the basal-like subset, whereas most of the other cancers were luminal, and the basal-like cancers were associated with increased invasion and shorter disease-specific survival.”

“In addition, as is being appreciated in patients with lower-tract cancers, patients with UTUC basal-like cancers may benefit more from immunotherapy, whereas patients with luminal cancers might benefit more from targeted therapies, such as FGFR inhibitors (drugs that slow cell growth) or antibody-drug conjugates.” This work was published in the *Journal of Urology*. ■

The Brady Trains Urology's Leaders: Pierorazio, Bivalacqua Head to Pennsylvania

A key part of The Brady's mission is to train the next generation of leaders in the field of Urology, and this year marks the departure of two of our most successful trainees and faculty members: Phillip Pierorazio and Trinity Bivalacqua.



PIERORAZIO TAKES HELM IN PHILADELPHIA

Phillip Pierorazio came to The Brady as a resident, after earning his M.D. at Columbia University College of Physicians and Surgeons – and his promise was evident early on, recalls urologist Patrick Walsh, M.D. In fact, Walsh mentioned it in a 2008 PBS interview with Charlie Rose <https://charlierose.com/videos/11761>: “I was asked what it takes to be a great surgeon. I told him that you had to be born with the right stuff.” Rose asked when this quality could first be recognized: “I said, ‘the day they walk up to the operating table as a medical student or intern,’ and mentioned that this week I worked with an intern like that. That person was Phil.”

Pierorazio is the new Chief of Urology at Pennsylvania Presbyterian Hospital, where he is building an Integrated Urologic Oncology program; and establishing a Men's Health and Reconstructive Urology program, as well as outreach clinic for the urologic care of the nearby community surrounding the hospital, situated in west Philadelphia. “Academically, I will be building programs in Kidney, Testicular and Upper Tract Urothelial Cancers,” he says, “in addition to a Cancer Survivorship Program similar in vision to those established at Hopkins over the past few years.”

Pierorazio leaves the Brady knowing that nobody ever really leaves the Brady, which forges a lifetime of collaboration: “It is my hope to continue the tremendous academic relationships we have built over the past 15 years of my time at Hopkins, and I hope the combined resources of both institutions can make a dramatic impact on the care of patients with urologic cancers.”



BIVALACQUA JOINS UNIVERSITY OF PENNSYLVANIA FACULTY

Last year in *Discovery*, we reported that Trinity J. Bivalacqua, M.D., Ph.D., the former *R. Christian B. Evensen Professor of Urology* and Director of Urologic Oncology, had received the Gold Cystoscope Award, one of the highest honors awarded by the American Urological Association (AUA). The award recognizes a young urologist who has made the most contributions during the first 10 years after completing residency. Recipients of this award, including many Brady faculty and former residents, have a distinguished history of going on to become leaders in the field – and this is what has happened.

This fall, Bivalacqua joined the faculty at the Perelman Center for Advanced Medicine and Penn Medicine Abramson Cancer Center at the University of Pennsylvania Department of Urology. He serves as the Director of Urologic Oncology, Vice-Chair of the Urology Department and head of the GU Cancer Service Line at the Abramson Cancer Center.

“Trinity Bivalacqua defines a translational surgeon-scientist,” says Alan Partin, Director of The Brady. Bivalacqua came to the Brady for his Urology residency after earning his M.D. and Ph.D. degrees from Tulane University's School of Medicine. After his fellowship, he joined The Brady faculty, where he became a leader in the fields of urologic oncology and sexual medicine. Bivalacqua headed a translational research program in genitourinary cancers and tissue engineering. His Brady lab developed the first preclinical model to study non-muscle invasive bladder cancer, and to originate novel intravesical therapies. The team also developed a tissue-engineered conduit that may one day lead to development of a new artificial bladder. More recently, his laboratory genetically re-engineered BCG to overexpress STING (stimulator of interferon genes). This new therapeutic will soon be used in patients with BCG-unresponsive non-muscle invasive bladder cancer.

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Prostate cancer runs in families more than any other cancer. Hereditary prostate cancer was discovered at The Brady, and for three decades we have worked to understand the genetics and molecular biology of the disease, and to develop more effective diagnostics and treatments.

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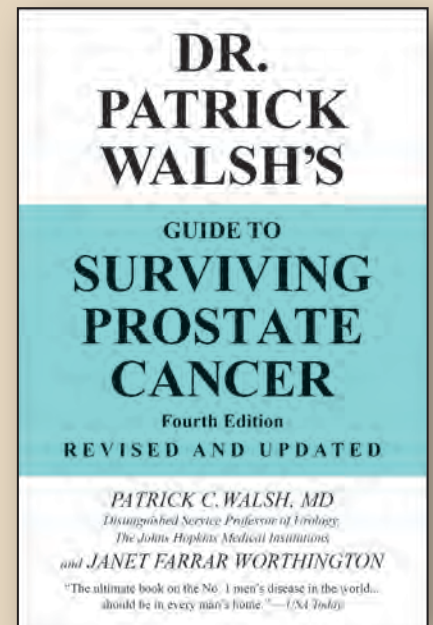
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