

# DISCOVERY

VOLUME 19 | WINTER 2023

*“Gifted Surgeon,  
Charismatic Leader.”*

**Mohamad E. Allaf, M.D. is  
Named the Brady’s New Director**



## INSIDE THIS ISSUE

- Genetic Risk Score in Black Men .....6
- Gleason 6: Not “Not Cancer”..... 11
- A PSMA for Kidney Cancer? ..... 16
- Neoadjuvant Chemo in MIBC..... 18

## FOUNDERS' CIRCLE

Partnerships with donors make discoveries possible. Thank you to those who have committed \$500,000 or more to The Patrick C. Walsh Prostate Cancer Research Fund.

Anonymous (3)  
Mr. and Mrs. Robert B. Aikens  
The Ambrose Monell Foundation  
Mr. and Mrs. Robert Baker Family Foundation  
Mary Ann and Bill Becker  
George and Mary Nell Berry  
Dr. and Mrs. Peter S. Bing  
Mr. Keith L. Bremer  
Elva E. and William W. Carty  
Jennifer A. Chalsty  
John S. Chalsty  
Mr. John Cook  
Deeks Family Foundation  
R. Christian B. Evensen  
Mr. Donald E. Graham  
Phyllis and Brian L. Harvey  
Heather C. and Patrick Henry  
Charlton C. and F. Patrick Hughes  
Nancy and William Kimsey  
Edward B. Lipkin  
Beverly A. and Gary L. McDonald  
Jean and Ian MacKechnie  
Beth W. and A. Ross Myers  
Nancy and Jim O'Neal  
Jack W. Shay and Thomas C. Quirt  
The Frank E. Rath Spang & Company Charitable Trust  
Mr. and Mrs. Paul W. Sandman  
The Peter Jay Sharp Foundation  
Irene and Bernard L. Schwartz  
Virginia and Warren Schwerin  
Donald and Susan Sturm  
Carolyn and Bill Stutt  
Mr. and Mrs. Charles B. Thornton, Jr.  
Luciana and Joe Vittoria

For additional news and updates from the Brady, please follow us on our web site at [hopkinsmedicine.org/urology](http://hopkinsmedicine.org/urology) or any of our social media sites:  
Facebook: Brady Urology;  
Twitter & Instagram: @brady\_urology



## HELLO!

If my face and name are familiar to you, it's because I have been at Johns Hopkins since I was 18 years old. I grew up here, and as you'll read in the story on page 2, I have been mentored by the best urologists in the world, including Patrick Walsh, Louis Kavoussi, and Alan Partin.

The Brady has an unrivaled legacy as the home of world-class Urology, and I am proud to be its new Director. We have packed these pages of *Discovery* with news about some of our most important initiatives — and we have barely scratched the surface! This is a vital, exciting place, and I hope we can convey some of the energy, enthusiasm and dedication you'll find here at the Brady.

In this issue, you'll read about genetic insights into the causes of life-threatening prostate cancer in Black men (pages 5 and 6), a beautiful friendship between a doctor and his patients (page 10), gut bugs and metastatic prostate cancer (page 12), exercise, immunotherapy and metastatic kidney cancer (page 16), and DNA damage-repair gene mutations in bladder cancer (page 18). And much more!

Our faculty and staff are committed to making life better for our patients. Their work is excellent, and I am proud to share it with you.

A handwritten signature in blue ink that reads "Mohamad E. Allaf". The signature is fluid and cursive.

MOHAMAD E. ALLAF, M.D.  
*Jakurski Family Director*  
*The James Buchanan Brady Urological Institute*  
*Johns Hopkins Medicine*



## COVER STORY

# “I Believe in This Place!”

An interview with the Brady’s new Director, renowned surgeon-scientist Mohamad E. Allaf, M.D.

Last year, *Discovery* reported that Alan Partin, M.D., Ph.D., was stepping down as Director of the Brady after 17 years, and that a national search was under way for his successor, who would become the Brady’s fifth director. In addition to Partin, previous Directors have been Hugh Hampton Young, William Wallace Scott, and Patrick C. Walsh.

Wonderful news! The best candidate for this big job turned out to be one of our own, and he is a familiar face to readers of *Discovery*: Mohamad “Mo” E. Allaf, M.D., previously Director of Minimally Invasive and Robotic Urologic Surgery.

You may know that Allaf is nationally renowned as a gifted surgeon and thoughtful scientist. What you may not know is the story of how he came to the Brady, a story that goes back 32 years.

## MIDNIGHT FLIGHT

Allaf’s family is Lebanese, but because of a civil war that tore apart the country, they moved to Kuwait to make a better life for their family. “Neither of my parents was college-educated,” says Allaf. “My sister was accepted into Bryn Mawr College,” in Pennsylvania. “My parents supported her in this. We all came with her,” to get her settled in the U.S., and the plan was to fly back to Kuwait in a few days. “We flew out at 1:15 in the morning on August 2, 1990,” Allaf says, “and then Iraq invaded Kuwait around two in the morning. We were on the last flight out.” Unable to go back to Kuwait, and unable to return to Lebanon, “we made the decision to stay here.”

It was not easy. Allaf was 16, and his world had changed radically overnight. He enrolled as a junior at Lower Merion High School, in a suburb of Philadelphia (he just missed basketball legend Kobe Bryant, who graduated from Lower Merion five years later). When Allaf graduated, “Johns Hopkins University took a chance on me.”

He came to Hopkins to study biomedical engineering. “While I was in a course as an undergraduate, I met Dr. Walsh, and became inspired,” not only by the field of Urology, but by the field’s early embracing of technology. Urologist Louis Kavoussi (now Chair of Urology at Northwell Health in New York) was an early pioneer in minimally invasive approaches to urologic surgery. “He became a mentor, in addition to Dr. Walsh. I did research with them as an undergraduate, then was admitted to medical school at Johns Hopkins – how can you turn that down? – and then was accepted to residency at the Brady.”

Alan Partin became Allaf’s mentor in academic leadership, providing the best of both worlds: “Patrick Walsh was my surgical mentor. I modeled my surgical approach on his meticulous dissection and excellence in outcomes. Alan really mentored me from an administrative, executive leadership standpoint: dealing with people kindly and gently but still moving things forward. Their combined vision has helped me craft my own thoughts on the future of the field. It is not lost on me that there are big shoes to fill and a legacy of excellence to continue and advance.”

## SOME OF THE BRADY’S MOST IMPORTANT INITIATIVES INCLUDE:

### The Hereditary Prostate Cancer (HPC) Program

“Led by William Isaacs, it’s one of a kind. Many men with prostate cancer have fathers, uncles, brothers, and sons who also have the disease. Understanding the underpinnings of HPC started with Drs. Walsh and Isaacs, and thanks to our donors, it’s been an amazing group effort to get to where we are now. We’ve built the infrastructure required to unlock those questions, and we need to double down and use our data in different ways.” How? Keep reading!

### Precision Medicine

“We are emerging into the era of big data and data analytics – combining our

unique biorepository of tissue and urine from thousands of men with prostate cancer with machine learning and artificial intelligence,” to make sense of millions of pieces of information.

Here’s an example: Say you are a 62-year-old Hispanic man with a PSA of 3.1, no family history of prostate cancer. You have Gleason 4+3 cancer in 3 of 12 biopsy cores and 70 percent Gleason pattern 4, with one nodule seen on MRI, a PI-RADS of 3, and a PSA density of 0.16. What is your likelihood of having PSA recurrence in five years? How successful has treatment been in other men with cancer like yours? Big data can answer these questions.

“The Partin tables were an early version of this; they looked at three things – Gleason score, PSA, and clinical stage – to predict whether cancer would be localized to the prostate. Today, all of the genomic data we have – no human can look at all of that and unlock it. Similarly, in clinical care, our MRIs and radiologic data are packed with quantitative information. Being able to integrate it through computers will allow us to make better decisions with more certainty for our patients. This is an important pillar for our patients moving forward – not just in prostate cancer, but in bladder cancer, kidney cancer, and other urologic diseases.” This is precision medicine. Johns Hopkins has 16 Precision Medicine Centers of Excellence (PMCOEs), and two of them are in Urology: one in prostate cancer, and one in bladder cancer. “In Urology, there are a lot of questions and uncertainty where decisions have to be made, and if we could use data to personalize those decisions for the patient in front of us, we would all be in a better place.”

*Continued on the next page >*

## ON THE COVER

Allaf is “a gifted surgeon and a charismatic leader,” says Patrick C. Walsh, M.D., the Brady’s third Director. “The Brady is fortunate to have him as our fifth Director!”



**Allaf:** “I want to do what Johns Hopkins did for me: Give me someone who’s smart, hardworking, and I will help that person succeed. I believe in this place!”

### Training Students and Residents

How do you train doctors in today’s era of so much information? One new tool: a surgical version of flight simulation. “The Halsted method,” pioneered by Johns Hopkins’ first Professor of Surgery, William Halsted, “was ‘see one, do one, teach one.’ See an operation, do an operation, and teach the operation. But now we need to evolve, so it’s not just an apprenticeship, but medical students starting early, doing robotic surgery using augmented reality, or even 3-D printed models.” Now, using 3-D printing technology, it is possible to make a model of someone’s actual organ, “and then create that organ using novel hydrogels,” using red dye in artificial blood vessels and “pressurizing it, so it behaves just like an artery would behave.” Allaf envisions having residents train on such models. “Just like in flight simulation: by the time they get to the OR, they are seasoned, having ‘flown’ many hours.”

### Combining Data and Technology to Improve Surgery

The Brady is fortunate to have had one of the first URobotics Labs in the world, headed by Dan Stoianovici, Ph.D. “Dan can help develop this augmented reality, using computer vision during surgery.” What is computer vision? Consider the smart phone, Allaf says. “If the iPhone can recognize what you look like, why can’t a robot machine recognize things during surgery that will aid me in a better surgery? For example, say there’s a small blood vessel that appears on the screen as I am doing robotic surgery. And the computer knows, based on the last thousand surgeries, that this has the potential to bleed two days later – it has the appearance of a complication in the making. Using data

analytics and computer vision, we can prevent this future problem in real time.”

Or, why not add a cancer-targeting tracer to the mix during surgery? What if there is a chance that cancer has moved past the prostate but is still curable with surgery? “We are doing a clinical trial right now using an injectable tracer, based on PSMA, that we can see during surgery.”

### “Expanding the Footprint” of Johns Hopkins Medicine

Johns Hopkins Medicine has expanded beyond Baltimore to Howard County, Suburban Hospital in Bethesda, and Sibley Memorial Hospital in Washington, D.C. The Brady has a very special relationship with Wellspan Health in York, Pa., and is now the exclusive provider of urologic care at their flagship hospital. We are able to provide access to Brady-level care through these points of access; in particular, at York and Sibley, we are growing our footprint in clinical care, offering research and clinical trials.”

What about places further away, “beyond the brick-and-mortar facilities?” Telemedicine! “A new infrastructure bill, signed earlier this year, will provide broadband internet to a big swath of the country that doesn’t have it. We are working to get our faculty licensed in some of these states.” This means that people who live in largely rural areas where medical care is sparse can have a consultation or get a second opinion in their own homes with a Brady urologist. Then, if they need treatment, they can make just one trip to a Hopkins facility. For example, say a man in Kansas, recently diagnosed with prostate cancer, would like to see Allaf: “I would review the biopsy, PSA, MRI,

and all the information in a telemedicine appointment. Then the next time we see each other could be the day of surgery: he could make one very efficient trip.”

### Schaufeld Program

“Five out of six men in Baltimore who die from prostate cancer are of African descent. The Schaufeld Program is funding research that examines biological and societal factors that may help us understand why Black men get prostate cancer more frequently, have more aggressive cancer, and have poorer outcomes. Through this program, we are working with the community to spread the word about screening and health literacy in Baltimore City. This is also a pipeline program with trainees who come from under-represented backgrounds. With this experience and training, they have a better chance of getting into medical school to become the scientists, and perhaps urologists, of tomorrow. We are very proud of this effort, and would like to expand it through investment. Right now, it is funded for five years. We are always thinking about the community we serve and how we as a Urology department can help influence better outcomes.”

### Take-Home Message

“There’s so much we could talk about: entire areas of Urology that aren’t routinely covered in *Discovery*,” which is focused on urologic cancer. What else, then, should readers of *Discovery* know about the Brady’s new Director? That he believes in the Brady, and he loves it. “We are a department that provides excellent, compassionate, cutting-edge care. Dr. Walsh’s legacy lives on. I was trained by Dr. Walsh. He instilled in me that caring *for* patients starts with caring *about* the patients. I see my life dedicated to the Institute, just like his. Johns Hopkins is home for me. I’ve been here since I was 18 years old – since 1992. I grew up here. My wife, Kendall, is a faculty member at Johns Hopkins. We met at Hopkins. Our first son was a preemie who spent a couple months here in the NICU. I owe Hopkins a debt of gratitude: I want to do what Johns Hopkins did for me. Give me someone who’s smart, hardworking, and I will help that person succeed. I believe I owe the next generation of medical students and residents. I believe in this place.” ■



**The Isaacs Brothers:** William, left, and John, in the early 1990s.

## After 45 Years at the Brady, John Isaacs Retires

For anyone who has been around the Brady a while, the photo above should make you smile. It's two members of the distinguished Isaacs family: scientist William Isaacs, at left, and his brother, scientist John Isaacs, at right. Not pictured is John's late wife, Sally, a talented genetic epidemiologist who served as the coordinator of the Johns Hopkins Hereditary Prostate Cancer Study for more than 20 years.

In 2022, after a 45-year career at Hopkins, John T. Isaacs, Ph.D., Professor of Oncology and Urology, retired. John is a pioneer in the translation of basic science theory into clinical trials for lethal prostate cancer. Decades ago, he began doing science that no one else was attempting: finding ways to exploit the body's process of apoptosis (basically, cellular suicide) as a means of killing metastatic prostate cancer.

John came to Johns Hopkins Hospital at a very early age: he was born here when his father was a Johns Hopkins medical student. After earning his undergraduate degree from Hopkins and his Ph.D. in biochemistry from Emory University, he returned in 1977 as a postdoctoral fellow with the Brady's longtime director of research, Donald S. Coffey, Ph.D. In 1980, he joined the faculty in the Department of Oncology with a secondary appointment in Urology, beginning a long and illustrious career focused on the molecular biology of prostate cancer and its application to the development of designer drugs for treatment.

In pioneering studies with Coffey, he showed that resistance to androgen deprivation occurs because of clonal selection: that androgen-resistant cells continue to grow, unfazed by hormonal therapy, and eventually overtake the hormone-sensitive cells. In subsequent studies, he and colleagues defined the mechanism by which androgen deprivation kills cells through apoptosis, and then provided evidence for a metastasis suppressor gene.

John's work on experimental therapeutics was based on specific targeting of metastatic prostate cancer cells with delivery of toxins through molecular engineering. More recently, his work was based on the use of cyclic supraphysiologic testosterone (STP) to treat metastatic castration-resistant prostate cancer. The author of more than 300 papers, John served as Editor-in-Chief of the journal, *The Prostate*, for 20 years. He was Co-Director of the Division of Experimental Therapeutics at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, and Professor of Oncology, Urology, Cellular and Molecular Medicine, and Chemical and Biomolecular Engineering, at the Whiting School of Engineering.

John always ends his emails with one word: "Peace." This is what the Brady wishes him as he starts his next chapter. ■

## Newly Discovered Mutation on *HOXB13* is Linked to More Aggressive Cancer in Black Men

*Men with the X285K mutation are more likely to develop higher-grade cancer at an earlier age, and more likely to develop metastatic cancer.*

Three decades ago, Brady investigators William Isaacs, Ph.D., the *William Thomas Gerrard, Mario Anthony Duhon, and Jennifer and John Chalsty Professor of Urology*, and Patrick Walsh, M.D., characterized hereditary prostate cancer, and in 2012 Isaacs identified the first prostate-specific cancer susceptibility

gene: *HOXB13*. Isaacs' team found a mutation on this gene, called G84E, and discovered that men who inherit this mutation are three to six times more likely to be diagnosed with prostate cancer, particularly at a young age. For many years, a mutated *HOXB13* gene was thought to be a risk only for men of Nordic European descent, because the G84E mutation is absent in men of African ancestry.

However, in a study in Martinique, of 46 men of African descent, a new *HOXB13* mutation, called X285K, was found. "Little was known about this or other mutations in *HOXB13* that may play a role in prostate cancer susceptibility in Black men," says Isaacs. To find out more, Isaacs and colleagues sequenced the *HOXB13* gene in 1,048 Black men who underwent radical prostatectomy at the Brady. "We found seven new mutations. Six of them were seen only once, but we found the X285K mutation in eight patients! Furthermore, all the men who had this mutation had Gleason 7 or higher cancers and were diagnosed at an average age below 52."

Isaacs, Walsh and colleagues published this work in 2021, and other investigators have confirmed their results and expanded the characteristics of this mutation. "Now we know that carriers of the X285K mutation are much more likely to develop metastatic prostate cancer than men who don't have it," says Isaacs. "Only several other genes in the entire genome – including *BRCA2*, *ATM*, and *MSH2* – also predispose men with mutations in these genes not only to develop prostate cancer, but also to develop *more aggressive, life-threatening disease*."

Like other gene mutations linked to hereditary prostate cancer, this mutation is relatively rare, Isaacs says. But because of its "ancestry-specific occurrence and association with risk for more aggressive disease at an early age," X285K has potential as an important new prostate cancer susceptibility marker that will help identify Black men who will benefit from earlier and more intense disease screening." This work was supported by the Department of Defense and the Patrick C. Walsh Hereditary Prostate Cancer Program. If you would like to contribute to this important research, please contact the Brady Development Office at [bradydevelopment@jhmi.edu](mailto:bradydevelopment@jhmi.edu) or 410-955-8434. ■

## GSTP1: Could This Gene Be Linked to Cancer Death in Black Men?

Black men in the U.S. are nearly twice as likely to die of prostate cancer than White men. What accounts for this terrible statistic?

“Without question, better insights into the causes of life-threatening cancers in Black men – insights that lead to actionable interventions – are sorely needed,” says pathologist Angelo M. De Marzo, M.D., Ph.D. In recent and ongoing work, De Marzo and a team of Hopkins scientists may have found such an insight.

Along with oncologist William G. Nelson, M.D., Ph.D., Director of the Sidney Kimmel Comprehensive Cancer Center, scientist Srinivasan Yegnasubramanian, M.D., Ph.D., and epidemiologist Elizabeth Platz, Sc.D., M.P.H., De Marzo began to investigate a gene whose relationship to prostate cancer was first explored more than 20 years ago by Nelson: *GSTP1* (pronounced GST “pie”). Nelson and others at Hopkins showed that *GSTP1* – which normally is responsible for inactivating certain environmental toxins – was shut down in more than 90 percent of prostate cancers. Without this protector gene, Nelson found, it was easier for prostate cancer to grow and become aggressive.

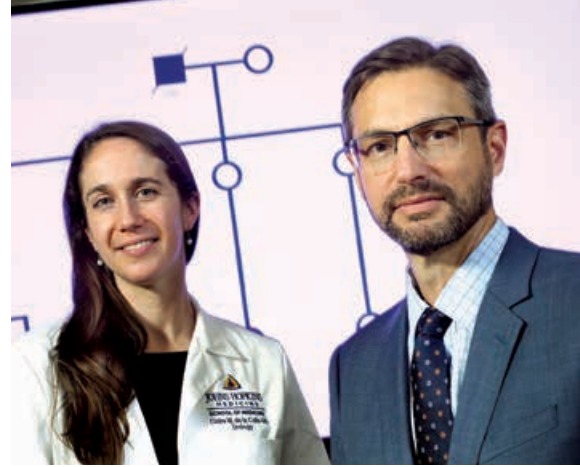
Recently, a research team led by De Marzo began looking at cancer tissue in the relatively rare instances when *GSTP1* is *not* knocked out, and what they found was startling: “Black men showed 2.5-3 times higher rates of having a *GSTP1*-positive cancer,” says De Marzo. Could the presence of this gene be linked to the higher risk of prostate

cancer death in Black men? To help answer this question, the team has launched a deeper investigation, led by Nelson, with funding from the Department of Defense Prostate Cancer Research Program (DOD PCRP). ■

## Prostate Cancer Genetic Risk Score in Black Men

The genetic risk score (GRS) is a different kind of genetic test: it doesn’t look for mutated genes that can lead to prostate cancer. Instead, it looks at genetic bits and pieces: single nucleotide polymorphisms (SNPs, pronounced “snips”). “SNPs are minor alterations in the human genetic code,” says urologist Claire de la Calle, M.D. “Individually, SNPs don’t have much of an effect, but when many SNPs are combined, they have been shown to be strong predictors of prostate cancer risk.”

Much of the pioneering work on SNPs has been done by molecular geneticist William Isaacs, Ph.D. at the Brady and by Jianfeng Xu of NorthShore University. Now Brady scientists, with colleagues at NorthShore and Northwestern University, have launched the GenBx trial aimed at validating the GRS in men of various genetic ancestral backgrounds. The GenBx trial is enrolling men with elevated PSA and will compare GRS with prostate biopsy results. “Our aim at Johns Hopkins is to focus on enrolling men of African ancestry,” says de la Calle, who with urologist Christian Pavlovich, M.D., the *Bernard L. Schwartz Distinguished Professor in Urologic Oncology*, was awarded a Schaufeld Program grant for this project. (For more, see Pages 7



**de la Calle and Pavlovich:** “It is critical to find better ways to identify high-risk men of African ancestry early on.”

and 14.) “So far, the test has mainly been calibrated in cohorts of patients of mostly European ancestry,” says de la Calle. “But it is critical to find better ways to identify high-risk men of African ancestry early on, as Black men are at higher risk of earlier and more aggressive diagnoses.” ■

## Precision Medicine: Genetics and Clinical Outcomes in Advanced Prostate Cancer

No two men with prostate cancer have exactly the same disease. Instead, each has distinct genomic and molecular changes that make the cancer more or less likely to respond to a particular treatment – and scientists still have much to learn about custom-tailoring the right treatment for each patient. A new Hopkins program may help.

“While there are attempts to develop new drugs specifically for patients with certain gene mutations, the clinical significance of these mutations is not well understood,” says medical oncologist Catherine Handy Marshall, M.D., M.P.H. With colleagues Mario Eisenberger, M.D., Emmanuel Antonarakis, M.D., Alex Baras, M.D., Ph.D., and systems engineer Arya Rasouli, Marshall developed the Genetics and Clinical Outcomes in Prostate Cancer (GCOP) Program, part of the Prostate Cancer Precision Medicine Center of Excellence. The program has a research library of biodata samples from nearly 500 patients.

“For example, PARP inhibitors are approved for the treatment of metastatic prostate cancer,” Marshall explains, “but which men might benefit the most, and who might not benefit, is still being studied.” ■

## Sidney Kimmel Comprehensive Cancer Center



**Yegnasubramanian, Nelson, Platz and De Marzo:** “This observation should prompt additional studies to determine whether *GSTP1*-positive cases represent a distinct molecular subtype of prostate cancer and whether *GSTP1* expression could provide a biological underpinning for the higher prostate cancer death rate in Black men.”

## Schaufeld Program Celebrates First Year

Last year in *Discovery*, we introduced an exciting new initiative, the Schaufeld Program for Prostate Cancer in Black Men, which addresses a critical issue: Black men are more likely to develop aggressive prostate cancer, and to die of it, than other men.

Many factors contribute, including genetic and environmental causes and disparities in health care, such as lack of early detection.

This program was established through the generosity of Brady philanthropists. It began with a \$5 million commitment from the Fredrick D. and Karen G. Schaufeld Family Foundation and has been strengthened by recent partnerships, including a new \$1 million investment to create an endowed research fellowship.

In its first year, the program established collaborations with leading universities; named five Schaufeld Scholars (post-baccalaureate students who contribute to the program's research and community outreach programs); and funded research projects aimed at understanding the mechanisms of prostate cancer, whose findings will not only help Black men, but *all* men with this disease.

The program has funded four important research projects so far:

**Genetic Risk Score in Black men with an Elevated PSA** (discussed in a separate story on this page.), **Claire de la Calle, M.D., and Christian Pavlovich, M.D., Principal Investigators.**

**Biological Differences as a Driver of Aggressive Disease, Tamara Lotan, M.D., Principal Investigator.** “We have been characterizing differences in a mark on the DNA called methylation in prostate tumors from men of African descent, comparing them to men of European ancestry,” says Lotan. Already, the research has brought to light an inflammatory gene called *IFITM3*, which is expressed at higher levels in Black men. “We are looking to see whether this correlates with inflammatory cell numbers in the prostate tumor. This may have implications for response to therapies such as immunotherapy.”

**Urinary Detection of Prostate Cancer, Jun Luo, Ph.D., Principal Investigator.** Luo's lab is investigating the use of a urine test to detect prostate cancer, collaborating

with Howard University investigators to increase enrollment of Black men in a clinical trial. “It is imperative that Black men be included in the study to ensure results are representative and applicable to all patients.” Luo hopes to expand this work to focus on early detection of aggressive prostate cancer in Black men through large-scale use of a urine test.

**Androgen Receptor (AR)-Mediated Regulation of Innate Immunity in Metastatic Prostate Cancer in Black Men, Janielle Maynard, Ph.D., Principal Investigator.**

Maynard and Elana Fertig, Ph.D., compared prostate tumors from Black men with those of White men and found some key differences in the expression of immune cells and AR-related genes. “Our initial data allowed for a new collaboration with Isla Garraway, M.D., Ph.D., Director of Urologic Research at UCLA,” to study other data available through the Veterans Administration system. Then, with Hopkins pathologist Angelo de Marzo, M.D., Ph.D., a study of metastatic prostate cancer tissue found that Black men had “more frequent AR loss, and that this affected innate immune cell expression, the body's first line of defense in fighting off enemy cells.” ■

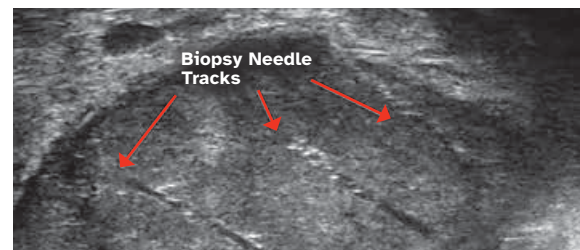
## Micro-Ultrasound: A New Approach to Prostate Biopsy

The image you're seeing at right is a prostate, and the lines on the picture are needle tracks from a prostate biopsy. This is not conventional ultrasound: it's micro-ultrasound (microUS), and its high-resolution images provide 300 percent improved clarity over conventional ultrasound. This is a new tool being studied and used by Gerald Andriole Jr., M.D., Professor and Director of Urology in the National Capital Region of the Brady Urological Institute. It was provided through the generosity of philanthropists Sandra and Larry Small and is available at Sibley Memorial Hospital.

MicroUS can be used along with MRI in a fusion biopsy or on its own in an ultrasound-guided biopsy, says Andriole. “Conventional ultrasound runs at 6 to 9 MHz, but this runs at 29 MHz. You see a lot more, down to the level of 70 microns – the width of a human hair! Andriole is one of the lead investigators in the ongoing OPTIMUM

trial, comparing microUS-guided biopsy on its own, MRI fusion biopsy, and MRI combined with microUS. “OPTIMUM will determine whether microUS can be used as an alternative to MRI/ultrasound fusion biopsy.” MRI is expensive and cumbersome, is not universally available, and is variable, depending on the age and strength of the MRI machine. MicroUS-guided biopsy can be done right in the urologist's office, with results available in real time. Brady urologist Christian Pavlovich, M.D., who was the first to use microUS for the prostate, is getting this updated version of microUS as well, and is the Principal Investigator of the OPTIMUM trial at Johns Hopkins.

The Brady is proud to welcome Andriole to our faculty. He is a nationally recognized clinician and scientist who has made major contributions to the field of prostate cancer screening and treatment. Andriole comes to the Brady from Washington University in St. Louis, where he was the Robert K. Royce Distinguished Professor of Surgery and Chair of Urology. This new position allows him to be closer to his wife, Dorothy, who is the Senior Director of Medical Education Research at the Association of American Medical Colleges in D.C. It is also a homecoming: “It's sort of full circle for us,” he says. “We were both fellows at the National Cancer Institute in the 1980s, and here we are again!” ■



**Andriole:** The OPTIMUM trial “will determine whether microUS can be used as an alternative to MRI/ultrasound fusion biopsy.”

## Turning Back the Clock on Treatment-Resistant Prostate Cancer

*If this hypothesis proves true, an LSD1-blocking agent could allow ADT and AR-blocking drugs to work again in men with mCRPC.*

Androgen deprivation therapy (ADT) and androgen receptor (AR)-blocking agents can hold prostate cancer at bay for a long time. But eventually, metastatic castration-resistant prostate cancer (mCRPC) develops; the cancer becomes resistant to these drugs.

“Neuroendocrine prostate cancer, a highly aggressive lethal variant, is emerging as an adaptive mechanism for resistance to AR pathway-targeting agents in mCRPC,” says scientist W. Nathaniel Brennen, Ph.D. “It is now recognized that many patients with advanced mCRPC have *mixed* disease,” with some cells that still respond to AR-targeting agents, and neuroendocrine cells that do not. Thus, next-generation therapeutic strategies “that can combat both subtypes co-existing within the same patient – often within the same tumor – are urgently needed.”

Brennen has identified a highly promising target: an enzyme called lysine-specific demethylase 1 (LSD1). “LSD1 plays a critical role in the epigenetic (reversible changes in gene activity) reprogramming required for this adaptive resistance,” he says. It is overexpressed in primary prostate cancer, and its production goes way up as cancer progresses to mCRPC. “LSD1 is directly implicated in prostate cancer proliferation and progression through both AR-dependent and -independent mechanisms. Therefore, we hypothesize that blocking LSD1 can reverse the epigenetic adaptation that is necessary to maintain this treatment-resistant status.” If this hypothesis proves to be true, an LSD1-blocking agent could, in effect, turn back the clock in prostate cancer, allowing ADT and AR-blocking drugs such as abiraterone and enzalutamide to work once again. It also may “prevent prostate cancer from developing the ability to survive in an environment without AR signaling.”

In collaboration with Hugh Young Rienhoff Jr., M.D., CEO of Imago Biosciences, Brennen is “evaluating a novel LSD1

inhibitor (Bomedemstat) for activity against prostate cancer.” To date, Bomedemstat has proven safe and well-tolerated in more than 200 patients with a variety of diseases, including acute myeloid leukemia. “Based on the robust activity observed in our preclinical models, particularly against the neuroendocrine subtype, we have teamed up with Drs. Adel Mandl and Michael Carducci to test this hypothesis clinically in patients with advanced mCRPC.” ■

## Prostate Cancer in Transgender Patients

*“Although it is quite rare, aggressive prostate cancer can occur in transgender patients on long-term hormone therapy.”*

Hopkins urologic pathologists are laying the groundwork for understanding prostate cancer in a very small population: male-to-female transgender patients. Because the prostate is not typically removed, these patients still need screening, and they can still develop prostate cancer.

“This was the largest to-date cohort of prostate cancer in transgender patients,” says pathologist Ezra Baraban, M.D., who was lead author of a study published in the *American Journal of Surgical Pathology*. In collaboration with scientists at Hopkins and institutions from across the country, Baraban and the study’s senior author, Jonathan Epstein, M.D., characterized the pathologic findings in a series of nine male-to-female transgender patients with an elevated PSA who underwent prostate biopsy; seven of them were diagnosed with prostate cancer.

The team correlated the pathologic features of the patients’ tumors with their history of hormonal therapy and their clinical outcomes after the diagnosis of prostate cancer. The study’s findings may help guide evaluation and treatment of prostate cancer in this population.

Some of the patients turned out to have metastatic prostate cancer – “indicating that although it is quite rare, aggressive prostate cancer can occur in transgender patients on long-term hormone therapy,” says Baraban. Another concerning issue relates to PSA. The hormone therapy that

some patients take significantly lowers PSA – which means prostate cancer might be missed because the PSA is too low to raise any warning flags. ■

## Low-Intensity Electro-stimulation May Improve Erectile Recovery

*“The implanted device enhanced nerve regeneration and function.”*

Low-intensity electrostimulation has been shown to enhance peripheral nerve regeneration. Can it stimulate regeneration in the nerves that control erection, and improve recovery of erectile function after prostatectomy? Arthur Burnett, M.D., the *Patrick C. Walsh Professor of Urology*, is leading a study to find out.

“Despite such modern advances as nerve-sparing techniques and robotic surgical technology, the cavernous nerves surrounding the prostate that are responsible for penile erection are invariably jarred at surgery,” says Burnett. “The phenomenon is often just temporary, and many men may recover erection ability in time – although recovery may be delayed for as much as two to three years, and in some cases erection recovery is incomplete.”

To help maximize recovery of these nerves, Burnett and his laboratory team are collaborating with Swiss colleagues, experts in bioengineering, at the Ecole Polytechnique Federale de Lausanne. In a rodent model of minor cavernous nerve injury that mimics the nerve trauma of nerve-sparing prostatectomy, these investigators surgically implanted a low-intensity electrostimulation device. Their results, published in the *Journal of Sexual Medicine*, are encouraging: “The implanted device enhanced cavernous nerve regeneration and function, and improved erection recovery,” says Burnett. Based on this promising study, the team is progressing toward clinical testing in patients at the time of prostatectomy. ■





**Burnett:** Honored for “groundbreaking advances in male sexual health, as well as advocacy, diversity and humanitarian contributions.”



**Patrick Walsh** with former Brady faculty, residents, and fellows at the annual meeting of the Society of Urologic Oncology, where he was recognized for his contributions to mentorship.

## Recent Brady Honors & Awards

**Arthur L. Burnett II, M.D., M.B.A.**, is the 2022 winner of one of the highest honors bestowed by the American Urological Association (AUA): the **Hugh Hampton Young Award**. Burnett was recognized for his “groundbreaking advances in male sexual health, as well as advocacy, diversity and humanitarian contributions.” Burnett is one of several former Brady residents or faculty to receive this prestigious award since its inception in 1971. Previous Brady recipients include Thomas A. Stamey, Frank Hinman, Jr., William J. Catalona, Mani Menon, Robert Gibbons, David M. Davis, and Patrick C. Walsh. The award was presented by then-AUA President Raju Thomas, M.D.

Burnett specializes in sexual medicine, major pelvic reconstruction, and the management of cancers of the genitalia and lower urinary tract, including prostate cancer. He also directs an active basic science laboratory. One of his major research contributions was uncovering the role of nitric oxide in erection – a discovery that led to the development of Viagra and other drugs. Burnett also founded and leads UroMissionsWorks Inc., a nonprofit organization that provides educational services for urology trainees in underserved populations worldwide.

**Patrick C. Walsh, M.D.**, the *University Distinguished Service Professor of Urology*, received **The Joseph A. Smith, Jr. Mentorship Award** from the Society of Urologic Oncology. This award was established in 2020 as an annual keynote address to be delivered as a tribute to Dr. Jay Smith, who embodied the spirit of mentorship in

the field of urologic oncology. Walsh is the second recipient of this award. During his 30 years as Director of the Brady, he oversaw the training of 62 residents: 87 percent went on to careers in academic medicine, and 23 of them became Chairs of major academic departments. In addition, his influence has shaped the entire field of Urology, especially in the care of patients with prostate cancer.

**Sean Fletcher, M.D.**, received the prestigious **Residency Research Award** (a \$10,000 prize) from the American Urologic Association for “Evaluating Use of a Genetic Risk Score in a Diverse Population to Improve Risk Assessment for Men on Active Surveillance.” Fletcher has been mentored during his research year by urologist Christian Pavlovich, M.D., and molecular geneticist William Isaacs, Ph.D.

**Shawn Lupold, Ph.D.**, the *Catherine Iola and J. Smith Michael Distinguished Professor of Urology*, has been elected President of the Society of Basic Urologic Research, a respected U.S.-based society with 600 active members in the U.S., Europe and Asia.

**Mohamad Allaf, M.D.**, the *Jakurski Family Director and Professor*, has been elected to the most prestigious urologic society in the world, the American Association of Genitourinary Surgeons, a highly select group of leading academic urologists.

Urologist **Marisa Clifton, M.D.**, Director of Women’s Health at the Brady, has been named the Associate Chief Medical Officer of the Johns Hopkins Hospital.

Urologist **Brian Matlaga, M.D., M.P.H.**, Director of the Stephens Center for Stone Disease at the Brady, has been

named the Executive Medical Director of Johns Hopkins International and Executive Vice Chair of the Brady.

Pediatric urologist **John Gearhart, M.D.**, the *Robert D. Jeffs Professor*, has been elected President of the Society for Pediatric Urology Surgeons, the most prestigious pediatric surgical society in the world, with only 25 invited members and limited to 10 from North America. This year the Brady will host the annual meeting.

### RECENT GRANTS

Scientist **Dan Stoianovici, Ph.D.**, Director of the Urology Robotics Program, has received NIH research support for his project, “Robot-assisted Personalized Prostate Biopsy.” **Jun Luo, Ph.D.**, received a \$1.1M grant from the National Capital Region Research Fund for his project, “Tracing the Disease Trajectory and Mutational Evolution of Metastatic Prostate Cancer.” **Mohamad Allaf, M.D.**, is serving as Principal Investigator along with Jim Hu, M.D., M.P.H., at Cornell and Brady alumnus Edward Schaeffer, M.D., Ph.D., at Northwestern, on two large NIH grants: He also is PI on a grant from Patient-Centered Outcomes Research Institute (PCORI), a nonprofit research organization, evaluating prostate biopsy and surgery techniques. **David McConkey, Ph.D.**, Director of the Greenberg Bladder Cancer Institute, received a Commonwealth Foundation grant to support his research in urothelial carcinoma. ■



**Dr. and Mrs. Misop and Susan Han with Toni Boucher, in center:** “I will cherish for the rest of my life the relationship I was able to build with Toni and Bud,” says Han.

## A Beautiful Friendship, and a Remarkable Gift

*“If he hadn’t been cured of his prostate cancer, he wouldn’t have been able to complete his work and have this opportunity to do good and fund the causes he most cared about.”*

Connecticut management consultant Henry “Bud” Boucher was diagnosed with prostate cancer by his local urologist, who recommended immediate surgery. Bud’s wife, Toni, said, “Not so fast.” The Bouchers came to the Brady for a second opinion with urologist Patrick Walsh, M.D., who recommended active surveillance. Misop Han, M.D., the *David Hall McConnell Professor of Urology and Oncology*, performed Bud’s follow-up biopsies and monitored his PSA.

“We did this for several years,” says Toni. “Over that period, we saw Dr. Han quite often and developed a warm relationship.” They talked about their families and about Toni’s work as a Connecticut state senator. When Bud’s prostate cancer needed to be treated, Han performed a prostatectomy. “Bud was cured of prostate cancer,” says Toni. “In fact, he was so well that afterwards, he got a term life insurance policy! More importantly, not only were we working with an outstanding surgeon, but a person of great kindness, compassion, thoughtfulness and faith.” The Bouchers came to trust Han’s medical opinion so much that when other medical issues came up, “he was the go-to guy,” who would connect them with the right Hopkins specialist. “That’s just who he is.”

In late 2020, “Bud had the biggest success of his life – just as he was about to give up – with the company that he had painstakingly worked with for 20 years,” says Toni. “We had always wanted to do philanthropic work, and the first person on that list was going to be Dr. Han.” Then, on Christmas Eve, a blood test suggested that Bud might have leukemia. Toni contacted Han. “He immediately responded to my text, at 9 at night.” Han got them in touch with Hopkins oncologist Douglas Smith.

“Bud was so excited, talking about Dr. Han and Dr. Smith, and our finally being able to give a gift that would be helpful to both of them.”

On January 26, 2021, late at night, Bud had difficulty breathing. Toni took him to the emergency room, and he died, very unexpectedly. “His heart just stopped,” she says. “I am grateful for the kindness and compassion that allowed my husband to feel a sense of hope and positivity right up to the very end. We had over a 55-year relationship that was a partnership in every way possible. We produced beautiful children and grandchildren – and I was a woman who didn’t want to get married and have children! I was squarely a career woman. He saved me from myself and in many ways, we saved each other. He was always thinking of the future. I’m so glad we were actually able to put it into reality. If he hadn’t been cured of his prostate cancer, he wouldn’t have been able to complete his work and have this opportunity to do good and fund the causes he most cared about. It was pivotal for us to develop a relationship with Dr. Walsh, the Brady, and Misop Han.”

The Bouchers’ generous gift to the Brady will support two research projects led by Han. One is in medical robotics. Han and Dan Stoianovici, Ph.D., are planning a clinical trial of the transrectal-guided robotic biopsy, based on a device Stoianovici created in the Brady Robotics Lab. “We will be enrolling about 1,000 patients over the next four years,” says Han, and the Boucher funding will support a postdoctoral fellow who will be working with Stoianovici. Han believes the robot’s 3-D visualization has the potential to perform just as well as or better than an MRI fusion biopsy.

The other project concerns the education of Brady residents. Han was the Urology Residency Program Director for eight years and then worked on safety and quality improvement for the Urology faculty. He also serves as Medical Director of the Johns Hopkins Hospital Credentials Committee. Han became interested in “making a connection between the resident evaluation, once they are done with fellowship training, and their success as an independent practicing physician.” Using data collected by the Accreditation Council for Graduate Medical

Education, Han is looking for ways to predict how young doctors will perform, “so the residency program directors can intervene before they graduate. This is a massive data project,” and the Boucher funding will support a statistician.

“As an educator, I have always believed in redemption,” says Han, “helping people to get better – for both patients and for physicians.” If a physician is struggling, “we want to intervene early on.” This project would not be possible without the Bouchers’ philanthropy. “We are tremendously grateful. I cannot thank Toni enough, and I will cherish for the rest of my life the relationship I was able to build with Toni and Bud.” ■

## Neoadjuvant Therapy and High-Risk Localized Prostate Cancer

*The next step is a multicenter randomized, placebo-controlled trial of Enoblituzumab.*

A protein called B7-H3, highly expressed on prostate cancer cells, has a detrimental effect on prostate cancer. As Hopkins scientists discovered several years ago, B7-H3 is associated with more rapid progression of prostate cancer after local treatment with surgery or radiation; it also suppresses the immune system’s ability to fight the disease.

But they found a way to block B7-H3: a monoclonal antibody drug called Enoblituzumab. Previously, *Discovery* reported on a small clinical trial: scientists Eugene Shenderov, M.D., D.Phil., F.A.C.P., and Emmanuel Antonarakis, M.D., gave Enoblituzumab to men with high-risk localized prostate cancer before prostatectomy and compared the men’s biopsy samples with prostate tissue removed during surgery. Their results were promising: men treated with six weeks of Enoblituzumab showed greater immune activity in their tumor microenvironment. They also had a drop

in their PSA levels and a decrease in their Gleason scores. Shenderov presented these results at the 2022 meeting of the American Society of Clinical Oncology (ASCO), and a paper is currently under review.

The next step is a multicenter, randomized, placebo-controlled trial, which Shenderov is planning with Mohamad Allaf, M.D., and colleagues.

In a related study, published in *Cancer*, Shenderov and pathologist Tamara Lotan, M.D., determined that there is increased expression of B7-H3 in men of African ancestry. “This may be one factor that helps explain why the disease is more aggressive in Black men,” says Shenderov. This study was among the first to use genetic ancestry markers “to add to emerging evidence that prostate cancer in men of African ancestry may have a distinct biology associated with B7-H3 expression.” ■

## Gleason 3+3=6 is Not “Not Cancer”

*“Grade Group 1 cancer has some of the same behaviors as higher-grade cancer. It’s invasive, and it can appear in perineural invasion and extraprostatic extension.”*

“Don’t worry about Gleason 3+3=6 (Grade Group 1)! It’s harmless! In fact, we shouldn’t even call it cancer!” Many patients have heard reassurances like these, and yes, if you have to have prostate cancer, Grade Group 1 is the best kind to have.

But wait: Let’s not call it “not cancer,” says Jonathan Epstein, M.D., the *Rose-Lee and Keith Reinhard Professor of Urologic Pathology*. “There are some very good reasons to keep the cancer designation for Grade Group 1.” Epstein should know; he is the renowned pathologist who came up with the Grade Group system of prostate cancer grading, a system that has been adopted worldwide.

“Under the microscope,” he explains, “Grade Group 1 cancer has some of the same behaviors as higher-grade cancer. It’s invasive, and it can appear in perineural invasion and extraprostatic extension,” cancer that has spread beyond the prostate but is still

curable. “Molecularly, it has many of the hallmarks of prostate cancer, as well.”

Another problem: many men who are diagnosed with Grade Group 1 cancer on biopsy turn out to have higher-grade cancer in their prostate, found at radical prostatectomy. “It was just missed during the biopsy.”

Epstein worries that if men believe they don’t have cancer, they won’t feel a strong need to get regular follow-up monitoring. “They may think, ‘My doctor said it’s not cancer, so why do I have to keep coming back?’” And yet, he warns: “The excellent prognosis of *treated* Grade Group 1 cancer is not the same if it is called noncancer and is not treated.”

A name change may not even be that meaningful today, Epstein continues. “Grade Group 1 is more intuitive to patients as low-grade cancer. With greater acceptance of active surveillance, patients are understanding that not all cancers are the same, that not everyone needs treatment right away – or ever – and that low-grade cancer can be followed carefully and safely.” ■

## Finding Metastatic Prostate Cancer that Doesn’t Make PSMA

*A small molecule that targets both FAP and PSMA? They’re on it!*

Two huge advances have dramatically changed the diagnosis and treatment of metastatic prostate cancer, and both of these involve prostate-specific membrane antigen (PSMA), a molecule that sits on the surface of prostate cancer cells. PSMA-targeting radiotracers, including a small molecule-based agent developed at Johns Hopkins (commercially available as PYLARIFY), allow a PSMA-PET scan to show where prostate cancer is hiding anywhere in the body – even as small as a grain of rice. And a different radiation-emitting particle attached to that same PSMA-targeting molecule (<sup>177</sup>Lu-PSMA-617, available as Pluvicto) tracks down these same cancer cells and kills them.

This is a whole new field called “radiotheranostics” (an approach using one radioactive drug to find the cancer, and another radioactive drug to treat it), and these are remarkable, highly promising

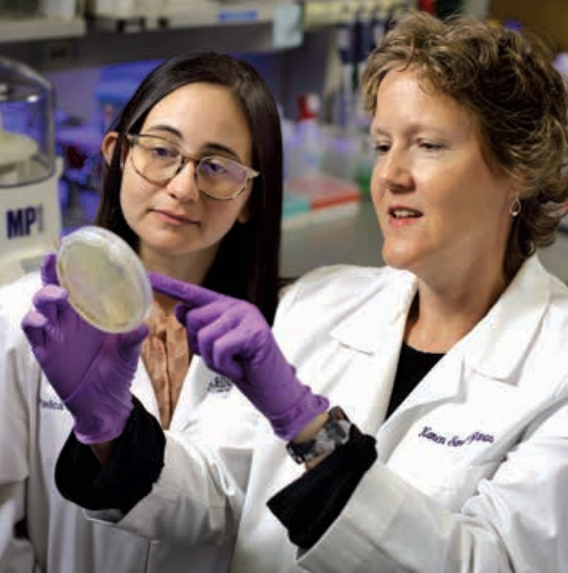
advances. But: although some people have had exceptional responses to PSMA-targeting radiotherapy, nobody is calling it a cure. It is a treatment that “has proven beneficial compared to the standard of care in metastatic castration-resistant prostate cancer (mCRPC),” says scientist Sangeeta Ray, Ph.D., M.S. With Martin Pomper, M.D., Ph.D., Director of Nuclear Medicine and Molecular Imaging, Ray has been working to develop new agents for molecular imaging and therapy for 17 years.

The problem, she explains, is that mCRPC is heterogeneous: it is made up of many different types of cancer cells. Some of these don’t make a lot of PSMA (which means the PSMA-targeting tracer can’t show where they are hiding), and some of them don’t make PSMA at all.

“Lesions that are PSMA-negative – for example, neuroendocrine prostate cancer – can represent particularly aggressive disease,” Ray notes. Fortunately, she and Pomper have found another target: Fibroblast activation protein alpha (FAP), another molecule that sits on these potentially lethal cancer cells. It is abundant, she says, and a characteristic of all mCRPC.

FAP-targeting small molecules have already been developed by the Hopkins team and others “for FAP-based PET imaging to detect PSMA-negative metastatic lesions.” What about a small molecule that targets *both* FAP and PSMA? They’re on it! “We hypothesized that a small molecule agent targeting FAP and PSMA might enhance cancer detection and therapy for targeting all prostate cancers, including those without PSMA, and neuroendocrine cancer. Such a strategy has the potential to overcome the limitations of current PSMA-radiotherapeutics.”

To test this hypothesis, the team developed an optimized agent (64Cu-FP-L1) attaching the FAP- and PSMA-targeting small molecules and tested them in relevant preclinical, experimental models of prostate cancers.” The results were exciting: “This new agent demonstrated high and specific tumor targeting of FAP and PSMA expression.” The next step is to see how well this dual-targeting agent will work as a potential treatment. Future studies are under way. This work was published in the *European Journal of Nuclear Medicine and Molecular Imaging*. ■



**Cruz-Lebrón and Sfanos:** Gut bacteria may actively undercut treatment of advanced prostate cancer.

## Gut Bugs and Treatment Response in Metastatic Prostate Cancer

*Even as medications work to suppress levels of male hormones, certain bacteria in the gut start their own hormone factory.*

In some cancers, such as melanoma, the population of bacteria in the patient’s gut can predict how well that patient responds to immunotherapy. “In fact,” says microbiologist Karen Sfanos, Ph.D., a pioneer in studying the interplay between bacteria and cancer, “high-fiber diets as a means to promote ‘good gut bugs’ and even fecal transplants are being studied in clinical trials as means to improve therapeutic response.”

But this may not work the same in prostate cancer. A recent study led by Lauren Peiffer, D.V.M., Ph.D., in Sfanos’ laboratory, investigated this phenomenon as part of a clinical trial led by Oregon Health & Science University scientist Julie Graff, M.D. Participants in the study were patients with advanced prostate cancer who had taken enzalutamide and were beginning treatment with an immunotherapy drug called pembrolizumab. Peiffer analyzed bacteria in fecal samples collected before and during treatment.

“Surprisingly, the study found that many types of bacteria that may affect immunotherapy in other types of cancer were not linked to treatment response in prostate cancer,” says Sfanos. “However, we identified different types of bacteria,” including a species typically found in the mouth called *Streptococcus salivarius*, “that were more

abundant in patients who had a response to therapy.” This study was recently published in the journal *Neoplasia*.

**Gut bacteria and hormone production:** Gut bugs may actively undercut treatment of advanced prostate cancer, and this is another major focus of Sfanos’ research. Even as androgen deprivation therapy (ADT) and androgen receptor (AR)-targeted treatment work to suppress levels of male hormones, certain bacteria in the gut start their own hormone factory! Gut bugs “can produce hormones that may interfere with hormonal therapy.” In 2018, Sfanos and colleagues reported that hormone-producing bacteria are more abundant in prostate cancer patients who are on ADT or AR-targeted therapy. A groundbreaking study by UK scientists recently confirmed these findings, and in mice with castration-resistant prostate cancer, they found a buildup of hormone-producing bacteria that make the disease worse.

The Sfanos lab has been collecting samples for use in microbiome studies since 2016. In one study, Sfanos, postdoctoral fellow Angélica Cruz-Lebrón, Ph.D., postbaccalaureate fellow Pedro Balbuena-Almodóvar, and collaborators are looking at clinical samples collected from prostate cancer patients undergoing treatment with abiraterone acetate (Zytiga). This project, funded by the Prostate Cancer Foundation and the Department of Defense Prostate Cancer Research Program, will measure hormone levels in fecal and serum samples as patients undergo treatment and will correlate these levels with treatment response. Ultimately, these studies aim to identify a microbial drug target that can make treatment for advanced prostate cancer more effective. ■

## Therapy Resistance in Cancer: Learning from Bacteria

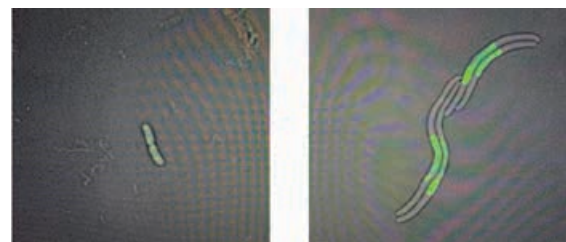
Why is metastatic prostate cancer so hard to kill? The short answer is that nobody knows. But scientists Kenneth Pienta, M.D., the *Donald S. Coffey Professor of Urology*, and Sarah Amend, Ph.D., have discovered at least one way that cancer cells manage to evade the consequences of systemic treatment: they sleep through it.

As reported previously in *Discovery*, Amend and Pienta discovered that cancer cells enter a “stealth mode,” called the polyaneploid cancer cell (PACC) state. They shut down and then wake up – unharmed – when the treatment is over. “This allows them to stop dividing, so they can avoid getting hurt by hormonal and chemotherapy treatments,” says Amend. To enter the PACC state, cancer cells “access a program that is present in virtually all species – including bacteria.”

George Butler, Ph.D., a postdoctoral fellow in Amend and Pienta’s laboratory, is using bacteria to study how organisms avoid treatments like antibiotics “so that we can better understand how cancer cells use these resistance programs,” says Amend. “This has the potential to open up a whole new area of research on how to cure resistant cancer.”

**In other work:** Pienta and Amend, looking for new biomarkers of prostate cancer that could be measured in urine and plasma, are focusing on extracellular vesicles (EVs). “EVs are nanoparticles that are secreted into biofluids such as urine and plasma by all living cells, including cancer cells,” explains Amend. “We are investigating them not only to understand their role in cancer development, but also because they may reveal valuable clinical information and have high potential as useful biomarkers.”

EVs can be difficult to study, but “our post-doctoral fellow Chi-Ju Kim, Ph.D., developed an assay that efficiently quantifies EV uptake through three-dimensional (3D) fluorescence confocal microscopy,” Amend says. “We published this protocol, including a step-by-step video, so that any scientist could use it!” This assay was described in the *Journal of Visualized Experiments*. ■



Here are *E. coli* bacteria with green fluorescent protein-labeled chromosomes. Left: Untreated control cells, small and rod-shaped. Right: The same bacteria after being treated with antibiotics. Somehow, they managed to survive, and scientists hope learning more about why this happens can shed light on treatment-resistant prostate cancer.

## Embryonic Genes Reactivated in Advanced Prostate Cancer

Embryonic genes are supposed to fulfill their mission before we are ever born and then shut themselves off. But somehow, metastatic castration-resistant prostate cancer (mCRPC) manages to reactivate these genes from our period of earliest development, says scientist Shawn Lupold, Ph.D.

“When these very specialized genes are turned back on, they can provide the immortality and adaptability needed for replication and transfiguration into different cell types,” he says. “In prostate cancer, these genes can be reactivated – possibly triggering the same immortality and pliability features – and this leads to therapeutic resistance.”

When does this happen? What’s the “on switch?” Which specific genes get reactivated? Lupold and colleagues in his laboratory, hoping to answer these questions, recently compared castration-sensitive prostate cancer cells with cancer cells that have become castration-resistant. They made an important discovery: “We found a specific group of embryonic genes, called homeobox or *HOX* genes, that become reactivated in castration resistant cells,” he says. Some of these genes, already known to be reactivated in prostate cancer, can be useful biomarkers for the initial diagnosis of prostate cancer. Using a combination of cell lines, human tissues, and RNA-sequencing technology, they found several additional *HOX* genes that are turned back on in a subset of metastatic and castration-resistant prostate cancers.

With this preliminary data, Lupold and his collaborator, Srinivasan Yegnasubramanian, M.D., Ph.D., applied for and received a three-year Idea Development Award from the Department of Defense Prostate Cancer Research Program. The goal is to delineate the role of these specific *HOX* genes in prostate cancer cell biology, metastasis, and therapeutic resistance.

In other news, Lupold, who holds the same professorship originated by the late, legendary Brady scientist Donald S. Coffey, Ph.D., is following in Coffey’s footsteps in another important way: he will soon serve as President-Elect for the Society of Basic Urologic Research,

and will become the prestigious group’s President in the fall of 2023. ■

## For Prostate Cancer Patients with Mismatch Repair Deficiency, Immunotherapy Alone?

*All patients in the study will receive nivolumab, a form of immunotherapy, without the addition of ADT.*

Bad things happen when the body’s DNA “quality control” mechanisms go awry. The job of these important genes, such as *BRCA2*, and proteins is to fix any errors that occur during DNA replications. When these “mismatch-repair” (MMR) functions are defective, “DNA mutations can accumulate,” says oncologist Mark Markowski, M.D., Ph.D., “and this can lead to cancer.”

As many as 5 percent of men with an inherited risk of prostate cancer have such a mutation. But this particular cloud may have a silver lining: “These tumors may be more susceptible to immunotherapy as a form of treatment,” Markowski says. Prostate cancer uses checkpoints – in effect, chemical handcuffs – to shackle powerful, cancer-fighting immune cells. Checkpoint-inhibiting drugs unleash these immune cells and are FDA-approved as an option for men with mismatch repair-deficient (dMMR), metastatic castration-resistant prostate cancer (mCRPC).

However, says Markowski, “these patients are already on androgen deprivation therapy (ADT), which has many side effects and has a significant effect on quality of life.” Is there a better approach for this very specific group of patients?

In other words: “Is hormone suppression necessary for immunotherapy to work in these men?” With oncologist Emmanuel Antonarakis, M.D., Markowski is studying whether immunotherapy *alone* can be an effective treatment for dMMR cancer at an earlier stage – when prostate cancer is still *hormone-sensitive* – “without the need for ADT.”

NIVO-BCR (NCT04019964) is a Phase 2 clinical trial for dMMR patients who have biochemical recurrence (a rising PSA) after

treatment for localized cancer with prostatectomy or radiation. “All patients in the study will receive nivolumab, a form of immunotherapy, without the addition of ADT.” This trial has enrolled six of the planned 15 patients, and early results are exciting, says Markowski: “So far, our research team has observed deep and durable clinical responses – including two complete responses.” In additional research, the team is also looking for key biomarkers that can help predict response and identify patients who may benefit the most.

If you are interested in learning more about this study, please contact Rana Sullivan via email: [tomalra@jhmi.edu](mailto:tomalra@jhmi.edu). ■



### LIFE-CHANGING CARE

This beautiful picture was suggested by a patient, who prefers to remain anonymous. At left is Renee Drew, CRNP, Nurse Practitioner for the Prostate Group, and at right is Kristen Farling, DNP, MS., Certified Urologic Nurse Practitioner (CUNP). “They need to be recognized!” says our patient, because they had a great impact on his quality of life.

“I was diagnosed, treated and cured of prostate cancer in 2021. Thank you, Brady! But the real story is the post-radiation therapy care provided by radiation oncology nurse Renee Drew and the Brady’s CUNP, Kristen Farling. Once a patient completes radiation therapy, there is a two-year period when side effects develop. In my case, I developed issues sustaining erections, and NP Farling immediately put me on injections. It changed my life! I am so grateful for these nurses’ dedication to my situation.”

We at the Brady are proud of the care we offer, and extremely proud of our nurse practitioners, who offer unrivaled and compassionate care.

## Read About the Research You Have Helped Make Possible.

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

How important is seed money? Priceless! Many of the scientists featured in this issue of *Discovery* jump-started their research careers with awards from the Patrick C. Walsh Prostate Cancer Research Fund. This great resource owes its existence entirely to patients: Patients made it happen! Patients of Patrick Walsh, M.D., who wanted to give back and help others who are going through prostate cancer. Patients and friends of the Brady who wanted to invest in the future, to help their sons and grandsons and those who love them.

Since its inception in 2005, this remarkable Fund has awarded millions of dollars to Johns Hopkins scientists in every discipline with good ideas worth pursuing. Their research has produced better ways to detect, treat, and prevent prostate cancer. Applications are reviewed by a Scientific Advisory Board comprised of noted Hopkins scientists and lay members. This year's awards are hot off the presses! We look forward to reporting on these exciting research projects as they unfold. Remember: *without you, their work wouldn't be possible!*

#### 2022 AWARDEES

**Christian Pavlovich, M.D.**  
*The Charlton C. and F. Patrick Hughes Scholar,*  
Department of Urology

**Jelani Zarif, Ph.D., M.S.**  
*The Beth W. and A. Ross Myers Scholar,*  
Department of Oncology

**Michael Carducci, M.D.,**  
*The George and Mary Nell Berry Scholar,*  
Departments of Oncology and Pathology

**Sushant Kachhap, Ph.D.,**  
*The Frank E. Rath Spang & Company Charitable Trust Scholar,*  
Department of Oncology

**Jun Luo, Ph.D.,**  
*The Virginia and Warren Schwerin Scholar,* Department of Urology

**Nirmish Singla, M.D., M.Sc.**  
*The Carolyn and Bill Stutt Scholar,*  
Department of Urology

**Shawn Lupold, Ph.D.**  
*The R. Christian B. Evensen Scholar,*  
Departments of Urology and Oncology

#### Genetic Risk Score: Determining Prostate Cancer Risk in Black Men

What's more accurate at predicting a man's prostate cancer risk than family history? His genetic risk score – obtained by looking at small variations in human DNA, called single nucleotide polymorphisms (SNPs, pronounced “snips”)? “We want to understand how individual genetics can influence the risk of a prostate cancer diagnosis,” says urologist Christian Pavlovich, M.D. “Unfortunately, most of the work in this area has been done in men of European ancestry.” Building on fundamental discoveries made by his research group, Pavlovich plans to extract DNA from stored blood samples from Black men who underwent prostate biopsy at Hopkins and consented to the storage of their samples. “We will compare this with clinical data to determine how genetic risk correlates with diagnosis of prostate cancer, and features of aggressive cancer on prostate biopsy or imaging.” ■

#### “Lighting Up” the Nerves Responsible for Erection During Surgery

The nerve-sparing radical prostatectomy is more precise than ever – but even so, many men struggle with erectile dysfunction, and “preservation of the nerves remains a challenge,” says urologist Nirmish Singla, M.D., M.Sc. If only there were a way to shine a spotlight on these nerves! Singla and his research group have come up with the next best thing: a compound that binds specifically to nerves that will “light up” with fluorescence during robotic prostatectomy. “We also developed an approach to administer the compound directly at the site, to enable rapid visualization of the nerves in real time during surgery,” he says. With this award, “we hope to develop and optimize a clinically translatable strategy to identify the nerves responsible for erections during robotic prostatectomy. We hope this work will expedite a first-in-human clinical trial of fluorescence-guided, nerve-sparing radical prostatectomy.” ■

## Making Immunotherapy Work Better in Advanced Prostate Cancer

Immunotherapy doesn't work nearly as well in prostate cancer as it does in other forms of cancer. Scientist Jelani Zarif, Ph.D., M.S., has identified a new target, "a protein that we found on the surface of cancer cells and immune cells in prostate cancer." The goal is to reverse tumor resistance to immunotherapy – first in "knockout mice" and then in human prostate cancer biopsy samples. They will look at the expression of this protein before and after treating the cells with Nivolumab, an immunotherapy drug. "We hope to enhance the effectiveness of immunotherapy in metastatic castrate-resistant prostate cancer, which is responsible for the deaths of more than 30,000 men each year in the U.S." ■

## Why Do Some Patients Respond to BAT?

Bipolar androgen therapy (BAT) uses something against metastatic castration-resistant prostate cancer (mCRPC) that sounds counterintuitive: high-dose testosterone. In small studies, some men have responded dramatically to BAT. One possible reason why: "We have recently published a finding suggesting that in patients who respond to this treatment, BAT is able to activate the immune system," says scientist Sushant Kachhap, Ph.D. Now, "our goal is to understand and define the molecular features of the tumors that respond dramatically to BAT therapy." Previously, Kachhap and his research team found that androgen receptor (AR) activity controls the cancer's response to BAT. To learn more, using human prostate cancer tissue samples, "we will employ an innovative labeling strategy to isolate and identify key regulators of AR function in prostate cancer. This would explain how AR reprograms the genes in response to BAT to bring about growth inhibition and immune cell activation." The team hopes to "uncover novel protein markers of BAT response which can stratify the

patients who will respond to BAT, and also to combine BAT with immunotherapy to achieve a better outcome." ■

## Understanding Biomarkers in Advanced Prostate Cancer

Genes called *long non-coding RNAs* (*lncRNAs*) have emerged as important biomarkers of prostate cancer – most notably, *PCA3*, found in urine and used to help determine the need for a prostate biopsy. But scientists still don't know exactly what these *lncRNAs* do in prostate cancer, says scientist Shawn Lupold, Ph.D. "It is critical to delineate the biologic mechanisms of these *lncRNAs*, because they may uncover new pathways and targets that contribute to prostate cancer progression and therapeutic resistance." With this award, Lupold will apply cutting-edge tools (called CRISPRa and CRISPRi) to activate and repress three *lncRNAs* (*PCA3*, *PCAT-1*, and *SchLAPI*) in human prostate cancer cell models. "The ultimate goal of this proposal is to delineate the role of each *lncRNA* in prostate cancer cell proliferation, invasion, migration, therapeutic resistance, and gene regulation." ■

## Studying a Variant of *HOXB13* in Black Men

*HOXB13* is a prostate cancer gene with two important variants: One, G84E, is found in men of European ancestry. The newly discovered second variant, X285K, is linked to a risk of aggressive prostate cancer in men of African ancestry. "X285K is quite possibly the most important marker identified to date for lethal prostate cancer risk in Black men," says Jun Luo, Ph.D. With this award, Luo will study the X285K variant in prostate cancer patients in Jamaica, a country with a high rate of prostate cancer, in pilot studies in collaboration with doctors in Jamaica. "Our findings will be used as preliminary data in NIH grant applications that will sustain this collaboration for long-term

studies. Knowledge on these heritable risk variants will benefit all men and their families, especially given the recent interest in using *HOXB13* as a therapeutic target." ■

## Targeting Neuroendocrine Prostate Cancer

Hormonal therapy is not able to control prostate cancer permanently. "Though initially successful, prostate cancer cells often become resistant to these drugs, leading to a more aggressive cancer type, called neuroendocrine prostate cancer," says medical oncologist Michael Carducci, M.D., *AEGON Professor of Prostate Cancer Research*. "Men with neuroendocrine prostate cancer often present with low PSA, high burden of disease, cancer that has spread to the liver and, unfortunately, does not respond to currently available treatments." But the research team of Carducci and scientist Nathaniel Brennan, Ph.D., has identified molecular pathways that run the cell machinery promoting neuroendocrine cancer. In a laboratory model, "our research has shown that inhibiting this pathway with an investigational drug slowed the growth of neuroendocrine prostate cancer." With this award, Carducci will conduct a clinical trial in men with advanced prostate cancer with neuroendocrine features. "Patients will receive bomedemstat, a Lysine Specific Demethylase 1 (LSD1) inhibitor that was initially developed for those with excessive platelet syndromes. This is the first trial of its kind in this unique prostate cancer patient population." ■



## KIDNEY CANCER PROGRAM: WORLD-CLASS CARE AND RESEARCH

The Kidney Cancer Program (KCP), jointly led by urologist Nirmish Singla and oncologist Yasser Ged, was established with the goal of offering world-class, multidisciplinary clinical care and cutting-edge collaborative research “to continuously improve the care of patients with kidney tumors around the world,” says Singla. “Our KCP team brings together expertise from Urology, Medical Oncology, Radiation Oncology, Nephrology, Pathology, Radiology, Immunology, Engineering, Statistics, and Epidemiology.” The program features six research subprograms, encompassing grant-funded clinical and translational research across the spectrum of kidney cancer. “We provide excellent, compassionate, personalized, multidisciplinary care for localized, locally advanced, and metastatic disease.”

## MORE BRADY UROLOGY CANCER NEWS

### DISCOVERY IN KIDNEY CANCER

## Kidney Cancer and Brain Metastases

*What causes this site-specific migration?*

Most people with kidney cancer don't have metastasis to the brain. But 15 percent of patients with advanced kidney cancer do, says urologic oncologist Nirmish Singla, M.D., M.S.C.S., Director of the Kidney Cancer Program. “These patients have traditionally exhibited poor outcomes, yet they remain largely understudied, both clinically and biologically. Although patients with brain metastases are among the most challenging to treat, they are often excluded from prospective clinical trials.”

What causes renal cell carcinoma (RCC) to move into the brain? Singla and neurosurgeon Chetan Bettegowda, M.D., Ph.D., the *Jennison and Novak Families Professor of Neurosurgery*, are determined to find out, looking for factors in RCC tumors that may be responsible for this site-specific migration.

“Our team is uniquely positioned to shed light on the biology of brain metastasis: we have a robust cohort of patients who underwent neurosurgical resection of at least one brain metastasis at Johns Hopkins,” with tissue available for analysis.

“By studying the molecular underpinnings of brain metastases, our research may help guide future biomarker discovery in bodily fluids to help monitor response to treatment in these patients. And by uncovering biological clues in metastatic tumors, we hope our findings may help guide clinicians in selecting more effective treatments for these patients.”

Singla is Principal Investigator of this study, funded by grants from the Kidney Cancer Association and the American Urological Association. ■

## Is There a PSMA for Kidney Cancer?

*A potential candidate for radiopharmaceutical therapy: GPNMB*

Readers of *Discovery* are likely familiar with PSMA, an enzyme that sits on the surface of prostate cancer cells. PSMA can be targeted for imaging with a radioactive tracer, and for treatment with a radionuclide – a radiation-emitting particle that can kill individual prostate cancer cells throughout the body.

Some forms of kidney cancer may have a similarly good target: Glycoprotein NMB (GPNMB). Like PSMA, this is a protein that sits on the surface of cells, and scientist Kaushal Asrani, M.B.B.S., Ph.D., aims to use this for detection and treatment of certain renal tumors: aggressive cancers that are driven by specific proteins called MiT and TFE.

“These proteins are known to promote renal tumors in translocation renal cell carcinomas (tRCC) and tuberous sclerosis complex (TSC),” says Asrani. “However, despite considerable advances in our understanding of MiT/TFE biology, we have not identified the mechanisms by which they drive kidney tumor formation, or leveraged this knowledge for their detection or treatment.”

There are no diagnostic biomarkers for tRCC, which can affect children, and there is no long-lasting treatment for TSC. However: In a recent study, published in the *Journal of Pathology*, “we showed that GPNMB expression is highly increased in tRCC and TSC, distinguishing them from other types of kidney tumors.”

In collaboration with George Sgouros, Ph.D., Director of the Radiological Physics Division, Asrani will determine whether “GPNMB promotes renal tumor formation in tRCC and TSC, and whether cell-surface GPNMB can be targeted for alpha-particle radiopharmaceutical therapy.” And if this proves to be the case: “We will create a highly potent and specific alpha-particle emitter, and evaluate its therapeutic potential in kidney tumor models of tRCC and TSC.” ■



## Exercise, Immunotherapy, and Metastatic Kidney Cancer

Kidney cancer loves obesity and doesn't like muscle. "Obesity is a known risk factor for renal cell carcinoma, and patients with renal cell carcinoma who have muscle mass loss have a less favorable prognosis," says medical oncologist Yasser Ged, M.B.B.S. In fact, recent studies have shown that these patients may not respond to immunotherapy.

Can this statistic be changed? A pilot clinical trial aims to find out. Ged is collaborating with Kerry Stewart, Ph.D., Director of Clinical and Research Exercise Physiology, and other investigators to study the effects of combining aerobic and resistance exercise with immunotherapy in patients with metastatic kidney cancer. "We will study the effects of a personalized exercise program in improving patients' quality of life and response to immunotherapy." Ged will also be evaluating changes in patients' muscle strength and density after combined exercise and immunotherapy. This pilot clinical trial is accruing patients. ■

## Managing a Tumor Thrombus in Kidney Cancer

"Some patients with renal cell carcinoma (RCC) display a unique pattern of local invasion known as tumor thrombus: the cancer invades the major vein that drains the kidneys and can potentially climb up to the heart," says urologic oncologist Nirmish Singla.

"Little is known about whether our approach to managing patients with tumor thrombus should differ based on the underlying histology," or how the cells look under the microscope. "While most RCCs are of a 'clear cell' histology, some cancers contain uncommon cell types, categorized as 'non-clear cell.'"

To address this, in a recent study, Singla and colleagues including Matthew Rabinowitz, B.S., a Johns Hopkins medical student, analyzed a group of 103 kidney cancer patients with tumor thrombi, 21 of whom had non-clear cell histology.

"Regardless of the cell type, our work shows that patients who had surgery to remove

the tumor exhibited similar outcomes and long-term survival," says Rabinowitz, the study's first author. "Our findings reassure us that selected patients with tumor thrombus should receive the same, rigorous surgical treatment irrespective of their tumor's histology." The study was published in *European Urology Open Science*. ■

### DISCOVERY IN TESTICULAR CANCER

## Testicular Cancer in Children

While testicular cancer represents the most common solid tumor in young men between the ages of 15 and 35, it is much less common in children – "and thus, children with testicular cancer are much more challenging to study," says urologic oncologist Nirmish Singla. "Unlike in adults, there are no reliable prognostic features to individualize risk of relapse among children with low-stage testicular cancer."

Singla, Director of the Testicular Cancer Program, recently led a multicenter analysis of three clinical trials from the Children's Oncology Group to identify predictors of outcomes in children with stage I testicular cancer. The investigators reported that children with early-stage disease demonstrated excellent survival outcomes, and the strongest predictors of relapse included older age and higher primary tumor stage.

"Children with low-risk testicular cancer are highly curable," says Singla. "Identifying predictors for relapse in these patients is important to inform personalized treatment strategies, while minimizing the risks and long-term toxicities associated with overtreatment." This work was published in *The Journal of Pediatric Urology*. ■



### DISCOVERY IN BLADDER CANCER

## A Novel Study for Patients with Small Cell Bladder Cancer

Small cell bladder cancer (SCBC) is aggressive and very rare; it accounts for less than 1 percent of bladder cancers. "Because it is so rare, very few trials have ever been done to determine the best way to treat it," says medical oncologist Jean Hoffman-Censits, M.D.

SCBC has more in common – in its behavior as well as its appearance under the microscope – with other small cell cancers than it does with other bladder cancers, says Hoffman-Censits. In fact, "recommended chemotherapy for SCBC is different than the standard chemotherapy for the more common urothelial bladder cancer, and is instead borrowed from the treatment approach to small cell lung cancer. Furthermore, our team and others have shown that mutations or changes that drive tumor development and growth, assessed by tumor genetic sequencing, look more similar between small cell lung cancer and SCBC, than do the changes comparing SCBC and urothelial bladder cancers."

Several studies have shown that combination chemotherapy with immunotherapy – checkpoint-inhibiting drugs – "is a safe and effective approach, leading to better outcomes than chemotherapy alone," says Hoffman-Censits. Checkpoint inhibitor therapy is FDA-approved for urothelial bladder cancer, although less is known about the effectiveness of these drugs in SCBC.

Hoffman-Censits and Hopkins colleagues are testing the combination of the FDA-approved checkpoint inhibitor, Atezolizumab, and standard chemotherapy in patients with newly diagnosed, localized SCBC. "Patients in this trial will begin therapy with intravenous chemotherapy and Atezolizumab, followed by surgical removal of the bladder. Ongoing postoperative atezolizumab treatment is planned to continue for a year to maximize the potential benefit of this approach." This important trial is enrolling patients in Baltimore and at Sibley Hospital. ■

**Hoffman-Censits:** "Small cell bladder cancer has more in common with other small cell cancers than with other bladder cancers."



Johns Hopkins faculty, fellows, residents, staff and students at the home of Erwin and Stephanie Greenberg (front row, center) for the Greenberg Bladder Cancer Institute's annual scientific retreat in May 2022.

## DNA Damage-Repair Gene Mutations and Neoadjuvant Chemotherapy in MIBC

Mutations in DNA damage-repair (DDR) genes – the best-known of these genes are *BRCA1/2*, linked to breast, ovarian, colon and prostate cancer – make it more likely that someone will get cancer, and get a more aggressive form of it. But there is a silver lining: certain drugs and forms of chemotherapy can target these mutations.

Two collaborative studies, both presented at the 2022 meeting of the American Society of Clinical Oncology, have shown that people with muscle-invasive bladder cancer (MIBC) who have certain DDR mutations respond well to neoadjuvant cisplatin-based combination chemotherapy. In this study, the DDR mutations were somatic: they happened because of the cancer. They were not germline, or inherited, mutations.

With investigators from Memorial Sloan Kettering Cancer Center, Fox-Chase Cancer Center, and other institutions, Greenberg Bladder Cancer Institute (GBCI) scientists Woonyoung Choi, Ph.D, M.S., and David McConkey, Ph.D., Director of the GBCI and the *Erwin and Stephanie Greenberg Professor of Urology*, performed the first prospective evaluation of the relationship between DDR mutations and response to cisplatin-based chemotherapy. This was done in conjunction with the Southwest Oncology Group's Phase 2 clinical trial comparing dose-dense MVAC chemotherapy (a combination of methotrexate, vinblastine sulfate, adriamycin, and cisplatin) to gemcitabine plus cisplatin. "In both arms of the trial, we confirmed that the presence of these mutations was associated with response,"

says McConkey, "particularly in patients with mutations in *ERCC2* or *ATM*." Choi is working with Fox-Chase scientists "to determine whether the inclusion of liquid biopsy measurements of tumor DNA in blood and urine can further enhance predictive accuracy."

In related research, McConkey, Choi, and colleagues looked at the link between mutations of *ATM*, *RBI*, *ERCC2*, and *FANCC* and pathologic complete response at cystectomy after neoadjuvant chemotherapy in patients with MIBC. "We believe this research can help guide the decision for bladder preservation in selected patients." ■

## Neoadjuvant Chemotherapy and Surgery for MIBC: What's a Successful Response?

Neoadjuvant chemotherapy is the standard of care for cisplatin-eligible patients with MIBC who undergo radical cystectomy (removal of the bladder). But there has been some controversy as to how to define a successful response to neoadjuvant chemotherapy. Should the goal be a "pathologic complete response" – in other words, no cancer left after surgery?

According to a recent Hopkins-led study, "There is mounting evidence to suggest that complete response as an endpoint may be reasonably broadened," says medical oncologist Noah Hahn, M.D., Deputy Director of the GBCI, "to include patients with residual non-muscle invasive disease at the time of radical cystectomy."

In this study, the investigators found that patients who still had some non-muscle-invasive cancer present after neoadjuvant

chemotherapy and surgery had "similar survival outcomes to patients with a complete pathologic response."

These findings were published in *Urologic Oncology*. ■

## Race, Ethnicity and Clinical Trials

There are significant differences in cancer – even the same type of cancer – among people of different racial and ethnic backgrounds. Understanding these genetic and molecular differences is critical in precision medicine.

However: "Racial and ethnic minorities have been vastly underrepresented in clinical research," says urologist Max Kates, M.D.

In a recent study, Kates and colleagues examined the reporting of racial, ethnic, and gender demographics of North American clinical trials for BCG-unresponsive, non-muscle-invasive bladder cancer, and compared this with the rate of new bladder cancer cases and deaths using data from the Centers for Disease Control and Prevention and the National Cancer Institute. They looked at 27 trials, published from 1994 to 2021, which enrolled nearly 1,700 patients.

"While all the trials included data on patient gender, only about 40 percent included any data on patient race or ethnicity." Of that 40 percent, the vast majority of participants – 94 percent – were white. Only 2.1 percent were Black, and 0.6 percent were Hispanic. "Black and Hispanic patients were significantly underrepresented relative to their proportion of new bladder cancer cases and deaths," says Kates. These findings were published in *Urologic Oncology*.

In a related collaborative study, Hopkins scientists reviewed 514 clinical trials performed between 1970 and 2020 to determine how many outcomes were reported based on race. They found that only 24 (4.4 percent) reported racial demographic data, and that the trials enrolled "strikingly low numbers of African Americans (2 to 8 percent) and Hispanics (2 to 5 percent). The results underscore the need to enroll these populations in future trials to address potential differences in clinical outcomes." This work was published in *Cancer Causes & Control*. ■

Everything  
grows when  
everyone  
gives.

Our commitment goes beyond today.  
With your help, we will be there  
for your children and grandchildren.

A gift from your will, trust, or retirement plan will help ensure the Brady Urological Institute remains a leader in advancing cancer research and making new discoveries for generations to come.

To learn more, contact  
the Office of Gift Planning:  
410-516-7954 or  
800-548-1268  
[giftplanning@jhu.edu](mailto:giftplanning@jhu.edu)  
[giving.jhu.edu/giftplanning](http://giving.jhu.edu/giftplanning)



JOHNS HOPKINS  
UNIVERSITY & MEDICINE



Discovery is published by

**THE JAMES BUCHANAN BRADY  
UROLOGICAL INSTITUTE**

**Johns Hopkins Medicine**  
600 North Wolfe Street, CMSC 130  
Baltimore, Maryland 21287-2101  
410.955.8434  
[www.hopkinsmedicine.org/urology](http://www.hopkinsmedicine.org/urology)

**Patrick Walsh, M.D.**  
*University Distinguished Service  
Professor of Urology Emeritus*

**Janet Farrar Worthington** *Writer/Editor*  
**Laura LeBrun Hatcher** *Design & Art Direction*  
**Keith Weller** *Principal Photography*

---

NON-PROFIT  
U.S. POSTAGE  
**PAID**  
PERMIT #1608  
BALTIMORE, MD

---

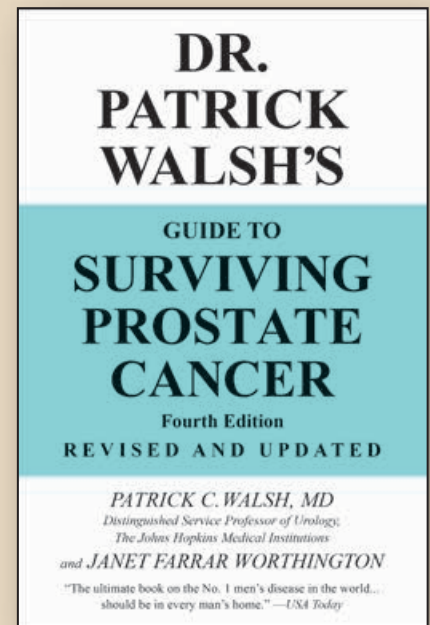
## Every Man Needs This Book.

**Each year, more than 160,000 American men are diagnosed with prostate cancer. The good news is that more men are being cured of this disease than ever before.**

**Fifth Edition Coming in 2023!** This lifesaving guide – Amazon’s #1 Bestseller in Men’s Health for 24 years – by renowned expert Dr. Patrick Walsh and acclaimed science writer Janet Farrar Worthington offers a message of hope to every man facing this illness.

Prostate cancer is a different disease in every man—which means that the right treatment varies for each man. Giving you a second opinion from the world’s top experts in surgery, pathology, urology, and radiation and medical oncology, this book helps you determine the best plan for you. **Learn:**

- What causes prostate cancer: your risk factors, including heredity, diet, and environment
- Why African American men are more vulnerable, and what they need to know
- Treatment considerations for gay and bisexual men with localized prostate cancer
- Why the digital rectal exam and PSA test can save your life—and how newer blood tests and imaging make the diagnosis more accurate
- New treatment guidelines that enable many men to safely undergo active surveillance and delay treatment
- Advances in radiation and surgery that save lives and reduce side effects
- Breakthroughs in the treatment of advanced cancers such as gene-targeted therapy and immunotherapy that are prolonging life and offering new hope



### FOURTH EDITION

***What you need to know about prostate cancer: Revised and updated with the latest advances in surgery, radiation, and precision oncology.***